

Hyperpolarized Xenon-129 Magnetic Resonance

Concepts, Production, Techniques and Applications

New Developments in NMR

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Hyperpolarized Xenon-129 Magnetic Resonance Concepts, Production, Techniques and Applications

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New Developments in NMR No. 4

Print ISBN: 978-1-84973-889-7

PDF eISBN: 978-1-78262-837-8

ISSN: 2044-253X

A catalogue record for this book is available from the British Library

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Preface

Since the first report of the NMR detection of ^{129}Xe in 1954 by Brun *et al.*, an amazingly broad scope of research efforts in xenon magnetic resonance has kept generations of scientists captivated with this apparently simple nuclear spin $I = 1/2$ system. Indeed, it is the simplicity of this mono-atomic probe that enables investigations of complex porous structures and the processes that take place within these porous systems ranging from materials science to the study of the complex nature of gas exchange in mammalian lungs. Many of the sophisticated applications have become feasible with the advent of hyperpolarized (hp) ^{129}Xe but also build on previous research with thermally polarized ^{129}Xe NMR spectroscopy. The experiments are of an inherently interdisciplinary nature and many of the key scientists who lead the way in the various aspects of ^{129}Xe magnetic resonance have contributed to this book.

The first two chapters, written by two of the pioneers of ^{129}Xe NMR spectroscopy, will shed light to the historical context but also explain in detail the one of most valuable assets of these methods – *i.e.* the ^{129}Xe chemical shift. Chapter 1 by Jacques Fraissard reviews the usage of the ^{129}Xe chemical shift in porous materials, while Chapter 2 by Cynthia Jameson explains the theoretical treatment of xenon chemical shift.

Chapters 3–7 review the methods of hyperpolarization starting with an introduction of some of the concepts and practicalities of spin exchange optical pumping (SEOP), to date the most important method to generate hyperpolarized (hp) ^{129}Xe . Chapter 4 describes the simulation of the processes in an SEOP cell, and William Hersman and co-workers review in Chapter 5 the most sophisticated design of a continuous flow SEOP apparatus available to date. Boyd Goodson and co-workers describe in Chapter 6 a batch mode (*i.e.* stopped flow) SEOP system. Long relaxation T_1 times are

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generally very important for all work with hyperpolarized spin systems as the hp state is generated outside the NMR or MRI magnet and then transferred into the sample or target organ. Brian Saam details the physical phenomena that cause ^{129}Xe T_1 relaxation in the gas phase but also on cell surfaces in Chapter 7. Very slow T_1 relaxation, for example, enables storage of the hp ^{129}Xe for some duration in between SEOP and actual usage of the gas.

Chapters 8–12 are highlighting recent applications of xenon to materials investigations, mainly with respect to porosity. Li-Qiong Wang describes in Chapter 8 how hp ^{129}Xe helps to study the pore structure and interconnectivity, *e.g.*, of ordered mesoporous compounds and electrode materials. In Chapter 9, Piero Sozzani and co-workers review ^{129}Xe NMR studies especially with respect to porous organic and hybrid materials. The fundamental concepts and applications of xenon cryoporology are explained in Chapter 10 by Jukka Jokisaari and co-workers. The usage of hp ^{129}Xe for the investigation of single-file diffusion – *i.e.* a diffusion phenomenon characteristic for narrow, elongated channels that exhibits a very different time dependence than unilateral diffusion in wider channels – is described by Russ Bowers in Chapter 11. Finally, Chapter 12 is devoted to the use of xenon to characterize adsorption-induced breathing transitions in flexible, *i.e.*, switchable metal–organic frameworks.

A fascinating development, pioneered by the groups of Alexander Pines and David Wemmer at UC Berkeley, is the use of hp ^{129}Xe entrapped in functionalized cage compounds for molecular imaging. Since the first conceptual studies in the late 1990's a number of groups have further advanced this xenon biosensor methodology. David Wemmer provides an introductory report about some of these developments in Chapter 13. In the following three chapters (Chapter 14–16), further key researchers, Patrick Berthault, Ivan Dmochowski, Leif Schroeder, and their respective co-workers, report about the amazing recent developments in this emerging area including biological cell studies.

Due to the limited supply of ^3He , pulmonary researchers are increasingly turning to ^{129}Xe for MRI of the lungs. Xenon's chemical shift, that is not available with ^3He , provides an additional incentive as it enables new insights in to pulmonary physiology in health and disease. Chapter 17 by Hideaki Fujiwara and co-workers describes how hp ^{129}Xe , administered for breathing in continuous flow mode, can be used for dissolved phase studies in animal lungs. Kai Ruppert and co-workers describe xenon uptake studies in human lungs in Chapter 18. Xenon septal uptake is reviewed from a different viewpoint focusing on different protocols by Samuel Patz and co-worker in Chapter 19. Xenon uptake in the lung leads to dissolved xenon in the blood. The ^{129}Xe chemical shift and relaxation behavior in blood is detailed by Jim Wild and co-worker in Chapter 20. Knowledge about transverse relaxation of xenon in lungs is crucial for MRI protocol development and is described by Giles Santyr and his co-workers in Chapter 21. Finally, dissolved phase xenon can also be used for MRI of the brain as Mitch Albert and co-workers explain in Chapter 22.

The final three Chapter belong to the 'Exotica' group as Chapter 23 introduces the reader to hyperpolarized noble gases with nuclear spin $I > 1/2$, namely another xenon isotope, ^{131}Xe and the only MR active krypton isotope, ^{83}Kr . Arnaud Comment explains in Chapter 24 why DNP may very well be the future methodology to produce hp ^{129}Xe . Finally, Joseph Granwehr illustrates in Chapter 25 that NMR and MRI detection of hp ^{129}Xe does not have to take place at the same location as radio frequency excitation and spatial encoding with pulsed field gradients.

The topics have been selected to provide the reader with a thorough, although not exhaustive, overview of current topics in hyperpolarized noble gas magnetic resonance. This book focuses on techniques and applications that utilize the ^{129}Xe chemical shift. Methods and applications that are more in line with hp ^3He methodology, such as apparent diffusion coefficient (ADC) measurement, are mostly left to the extensive literature in this field. We hope you will enjoy this book dedicated to magnetic resonance with ^{129}Xe – and, of course, with the occasional quadrupolar noble gas isotope.

Thomas Meersmann
Eike Brunner
Nottingham and Dresden

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CHAPTER 1

Xenon as a Probe Atom: Introduction, Characteristics, Investigation of Microporous Solids

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1.1 Introduction

The central idea of the pioneers¹ of this technique was to find a non-reactive molecule particularly sensitive to its environment, detectable by NMR, which could be used as a probe to determine microporous solid properties difficult to detect by classical physicochemical techniques in a new way.

The isotope ^{129}Xe is this ideal probe: spin 1/2, 26.4% concentration in xenon, fairly good detection sensitivity and very wide chemical shift range. The very large and extremely polarizable electron cloud of xenon makes this atom particularly sensitive to its immediate environment. Small variations in the physical interactions with the latter cause marked perturbations of the large and extremely polarizable electron cloud which are transmitted directly to the xenon nucleus and greatly affect the NMR chemical shift. The quadrupolar ^{131}Xe isotope, with spin 3/2, can also be used, but less easily, for certain specific applications. Now, by using optical polarization techniques

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

the sensitivity of detection can be increased by several orders of magnitude, which widens the field of applications of this technique.² Fragmentary reviews have already been published.^{3,4} In this chapter we will focus our attention mainly on ^{129}Xe NMR as a means of probing the properties of zeolites, adding only few words on other microporous solids.

Zeolites are crystalline aluminosilicates with open 3D framework structures consisting of SiO_4 and AlO_4 tetrahedra linked to each other by sharing all the oxygen atoms, to form regular intracrystalline cavities and channels of molecular dimensions, inside which cations, water and/or small molecules may reside. They are often also referred to as molecular sieves. This term refers to their ability to selectively sort molecules based primarily on a size exclusion process. This is due to a very regular pore structure of molecular dimensions. The limiting pore diameters are roughly between 3 and 10 Å. At present, over 130 different framework structures are known.⁵ In addition to having silicon or aluminium as the tetrahedral atom, other compositions have also been synthesised, including the growing category of microporous aluminophosphates, known as AlPOs.

Zeolites are used in a variety of applications with world production estimated to be about 3 million metric tons per year. They are used in many organic reactions (cracking, isomerization, alkylation), water softening and purification, in the separation and removal of gases and solvents, agriculture, animal husbandry and construction. They can also serve as oxidation or reduction catalysts, often after metals have been introduced into the framework. Examples are the use of titanium ZSM-5 in the production of caprolactam, and copper zeolites in NO_x decomposition.

1.2 Zeolites with a Single Type of Void Volume. Study of the Pore Structure

1.2.1 Notion of the Mean Free Path

Consider, first of all, zeolites containing only OH or cations having very weak interactions with the xenon, such as Li^+ or Na^+ . Most information is generally obtained by analysis of the variation of the chemical shift δ with the xenon concentration at different temperatures, usually at 300 K,^{1,4} according to eqn (1.1).

$$\delta = \delta_0 + \delta_s + \delta_{\text{Xe}} = \delta_0 + \delta_s + \delta_{\text{Xe-Xe}} \cdot \rho_{\text{Xe}} \quad (1.1)$$

δ_0 is the position of the isolated atom. This corresponds to virtually zero pressure. Figure 1.1 shows that each variation is characteristic of a zeolite^{4,6} and defines two parameters, the term δ_s at zero concentration and the variation δ_{Xe} corresponding to Xe–Xe interactions, $(\delta_{\text{Xe-Xe}})$, and which increases with the concentration, ρ_{Xe} , of adsorbed Xe as in the gas phase.⁷ δ_s depends on the dimensions of the cages or channels and on the ease of xenon diffusion in the crystallite. So the introduction of the mean free

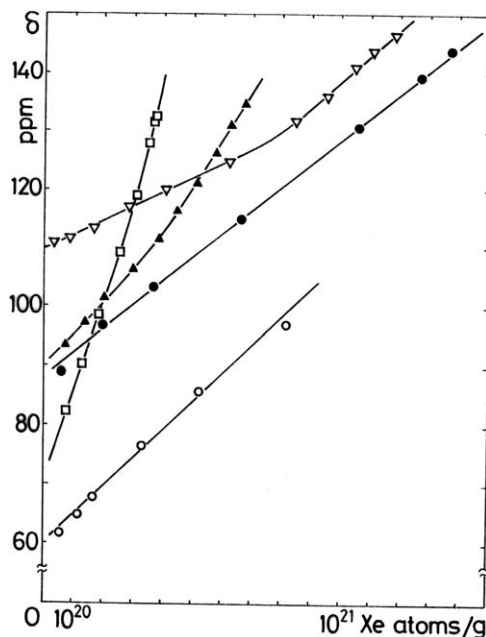


Figure 1.1 Chemical shift δ of adsorbed ^{129}Xe versus the number of Xenon atoms per gram of solid (one signal). ($\circ$) NaY; ($\bullet$) ZK4; ($\blacktriangle$) K-L; (∇) ZSM5; ($\square$) omega. (Reprinted from ref. 5, with permission from Elsevier.)

path, $\bar{\ell}$, imposed by the pore structure which is a parameter taking account of these two parameters. $\bar{\ell}$ is defined as the average distance travelled by a Xe atom between two successive collisions against the pore walls.

Exchange between adsorbed and gaseous phases being negligible for microporous solids at room temperature,⁸ the experimental chemical shift, δ_s , of one atom is the average value of the shift of xenon in rapid exchange between a position A on the pore surface, defined by δ_a (with probability N_a), and a position in the volume V of the cavity or channel, defined by δ_v (probability N_v).⁹

$$\delta_s = (N_a \delta_a + N_v \delta_v) / (N_a + N_v) \quad (1.2)$$

δ_a depends on Xe-surface interactions. δ_v is a function of δ_a and the distance travelled between two successive collisions against the pore wall, ℓ . In fact, $\delta_v = \delta_a$ when the atom leaves the surface; then δ_v decreases during the journey between two consecutive adsorption sites, whence the need to determine a mean value $\langle \delta_v \rangle = f(\delta_a, \bar{\ell})$.^{8,9} The plot of $\delta_s = f(\bar{\ell})$ for some classical zeolites is hyperbolic in shape, according to eqn (1.3) (see Figure 1.2-I):

$$\delta_s = (1/\lambda + \mu \bar{\ell}) \delta_a \quad (1.3)$$

λ and μ are fitting parameters. δ_a is related to the molecular interaction energy which depends on the surface curvature, hence on $\bar{\ell}$.¹⁰

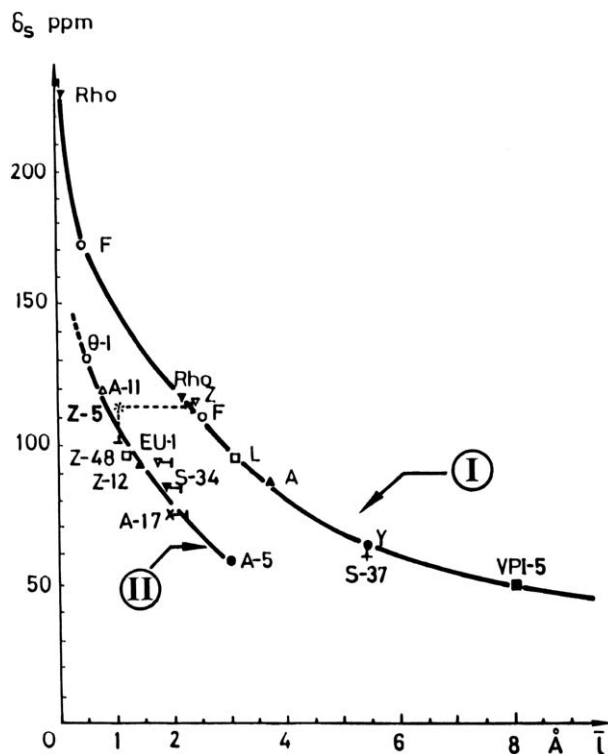


Figure 1.2 Chemical shift δ_s versus the mean free path $\bar{l}$. Curve I (classical zeolites): Rho (cavity and prism), Ferrierite: F (channels b and c), Mordenite: Z (main channel), L, A, Y. Curve II (other molecular sieves): Theta-1: θ -1, AlPO_4 -11: A-11, ZSM-5: Z-5, ZSM-48: Z-48, EU-1, ZSM-12: Z-12, SAPO-34: S-34, AlPO_4 -17: A-17, AlPO_4 -5: A-5, SAPO-37: S-37, VPI-5. (Reprinted from ref. 19, with permission from Springer.)

1.2.2 Influence of the Temperature and of the Surface Composition

The fast exchange model easily explains how the effect of the temperature depends on the pore size. $\langle\delta_v\rangle$ is slightly lower than δ_a if the mean free path, $\bar{l}$, is small or, on the contrary, much smaller than δ_a if $\bar{l}$ is large. The experiment temperature changes the residence time of Xe on the pore wall, so also the influence of $\langle\delta_v\rangle$. Therefore, the greater $\bar{l}$, the larger the influence of T . For example, in the range $150 \leq T \leq 390$ K, the variations of δ_s are 48 and 18 ppm for Y and ZSM-5 zeolites, respectively.¹¹

The chemical shift δ_s depends slightly on the Si/Al ratio. For example, when this ratio increases from 1.28 to 54, δ_s decreases monotonically by 4 ppm in the case of faujasite and by about 9 ppm for ZSM-5 and ZSM-11.⁴

The variation of δ_s with framework composition has been also reported for SAPO-37, AlPO_4 -5 and SAPO-5 molecular sieves.⁴ These deviations from the

simple model are responsible for the fact that many structures studied, mainly with very low cation content, do not fit the first $\delta_s = f(\bar{\ell})$ curve; they form a cloud of points limited by a second curve for $0.05 < \bar{\ell} < 0.4$ nm (see Figure 1.2-II).

1.2.3 Theoretical Models

Using the fast exchange model, Cheung *et al.*¹² expressed the chemical shift δ_s of xenon adsorbed in Y zeolites at temperature T as:

$$\delta(T, \rho) = \delta_s = [bn_a / (1 + bn_a)] \delta_a, \quad (1.4)$$

where $b = k_a/k_d$ is the ratio of the rate constants for adsorption and desorption of a xenon atom on a site, n_a the number of adsorption sites in a unit volume.

Cheung also determined an expression of $\delta_{s(T)}$ for different structures:¹³

$$1/\delta_{s(T)} = A_{(T)} + B_{(T)} (L - 2r_{Xe})/m \quad (1.5)$$

where $m = 1$: layer-like pore (clay); 2: cylindrical pore; 3: spherical pore.

L is the distance between leaflets ($m = 1$) or the pore diameter, and r_{Xe} is the radius of the Xe atom. $(L - 2r_{Xe})/m$ is the mean free path, $\bar{\ell}$, previously introduced experimentally.⁹ The terms A and B vary with the temperature, but the variation $\Delta\delta_{s(T)}$ of δ_s increases with the pore size, as was also shown experimentally.¹¹

Ripmeester and Ratcliffe considered the potential energy between a xenon atom and a spherical shell of radius R representing the cage wall.¹⁴ Oxygen atoms are smeared over this shell with a density similar to that of the zeolite A cage. Cheung made analogous calculations for a xenon atom trapped between two infinite parallel layers.¹³ From their calculations these authors concluded that for small cages or interlayer distances, δ_s values can be expected to reflect the true void space. However, for large cages or interlayer distances, δ_s is a complicated function of sorption energy, void space and temperature, the δ_s variations with temperature being a means of distinguishing the two types of behavior, in agreement with experiments.¹¹

1.3 Complex Zeolite Structures

1.3.1 Pure Zeolites

¹²⁹Xe-NMR spectra have as many components as there are different types of void volume in the zeolite structure, at least if exchange between xenon adsorbed in the different zones is slow on the NMR time scale. This is the case of ferrierite at 300 K whose spectra have two lines corresponding to the two types of channels.⁴

The spectrum of xenon adsorbed on Rho zeolite depends on the nature of the cation and on the temperature. For H-Rho at 300 K, there is rapid exchange between cavities and prisms. The two characteristic lines are then

obtained only at low temperature. On the contrary, for CsRho there is only one line, since the Cs cations are located in the prisms and prevent Xe atoms from being there. The flexibility of the Rho structure as a function of the temperature has also been studied.¹⁵ In the same way, the ^{129}Xe NMR spectrum of mordenite has two signals corresponding to one-dimensional channels connected to the side-pockets in the perpendicular direction, at least if the temperature is low enough to prevent exchange between these two sites.^{16,17}

1.3.2 Mixtures of Zeolites. Structural Defects. Crystallisation

^{129}Xe NMR is no longer used to determine the pore structure of a perfect zeolite, except to refine certain surface details or to check the interconnection between pores. But it yields valuable information on the structure of the gel and the mechanism of the synthesis during the crystallisation of the zeolites.^{18,19} Indeed Xe atoms are being used to probe the size of the cavities under formation, their modifications and the ultimate appearance of well-defined zeolitic materials. In addition, it can be used to follow the progression of the crystallinity.

This technique is also the best for the characterization of defects, whatever their nature. In the case of a mixture of zeolites or a structure intergrowth, each zeolite component gives rise to its own NMR lines in the spectra, provided that the diffusion of Xe between monocrystalline domains is not too fast and prevents the averaging of Xe-zeolite interactions; for example: synthetic mixture of Ca-A and Na-Y, ferrierite-mordenite intergrowth, ALPO4-8 structure in a VPI-5 sample, ZSM-5-ZSM-11 intergrowth in a ZSM-8 sample have all been analysed successfully.²⁰

Finally, this technique can characterize the structure defects, generally distributed randomly in industrial zeolites. For example, the two signals in Figure 1.3-left correspond to xenon in the supercages of a partly dealuminated Y zeolite and in a well defined secondary porosity corresponding to the volume of two adjacent supercages whose separation has been destroyed, respectively.²⁰ With the mordenite studied (see Figure 1.3-right) the

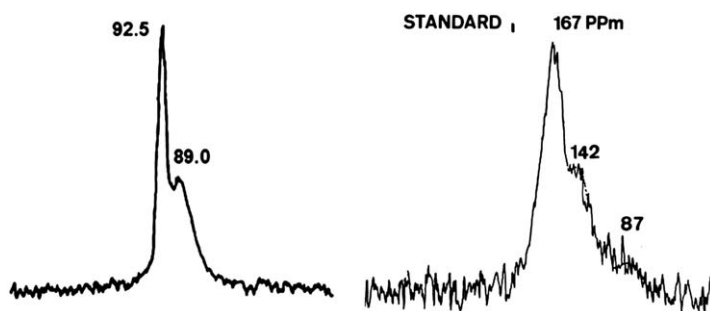


Figure 1.3 Room temperature spectra of xenon adsorbed in partly dealuminated zeolites Y (left) and mordenite (right).
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decrease in the chemical shift of the signal reveals a significant increase in the diameter of the main pore; the shoulders at lower δ correspond to the presence of various undefined but relatively large defects.

1.4 Influence of the Compensating Cations

The zeolites used in various applications most often contain xenon adsorption sites stronger than the surface, in particular more or less charged or voluminous cations. In this case the NMR spectrum depends on both the Xe-surface and Xe-other sites interactions. If the exchange between these various sites is fast with respect to the NMR time-scale (generally the case at 300 K), one average signal is observed, but the $\delta(T)=f(\rho)$ variation can provide much information about the nature of these sites and their distribution in the structure. To obtain more details it is enough to reduce the experiment temperature. Generally speaking the variation of the chemical shift with the adsorbed xenon concentration is given by eqn (1.6)

$$\delta = \delta_{\text{ref}} + \delta_{\text{s}} + \delta_{\text{Xe}} + \delta_{\text{SAS}} + \delta_{\text{E}} + \delta_{\text{M}} \quad (1.6)$$

where the last three terms correspond to: the Xe-cation interaction, δ_{SAS} , the effect of the electrical field, δ_{E} , and, if it exists, the magnetic field, δ_{M} , created by these cations. These three terms are negligible with H^+ , Li^+ or Na^+ .^{20,21} The $\delta(T)=f(\rho)$ plots for KY and RbY are parallel to the previous ones but the shift increases with their bulk: $\delta_{N \rightarrow 0}$ is 78 and 99 ppm, respectively. But the study performed on Y zeolites shows that δ depends not only on the number, the charge and the size of the cations, but also on their electronic structure.

1.4.1 Divalent Cations with d^0 Electronic Structure

In this case the large positive shift and the parabolic form of the $\delta=f(N)$ curves was attributed first to the distortion of the xenon electron cloud by the strong electric fields, δ_{E} , created by the $2+$ cations;^{4,6,20} but also, later, to the formation of a partial bond between these two species formed by the donation of a xenon 5p electron to the empty s orbital of the divalent cations.¹² The corresponding chemical shift $\delta_{N \rightarrow 0}$ is greater than in the case of an uncharged structure (influence of δ_{SAS}). When the xenon concentration N increases, δ decreases if there is fast exchange of the atoms adsorbed on SAS with those adsorbed on the other sites. When N is high enough, the effect of Xe-Xe interactions again becomes the most important and δ increases with N . This technique is particularly interesting for detecting cations which are really accessible to other adsorbed molecules. For example, in the case of $\text{Na}^+\text{Mg}^{2+}\text{-Y}$ or $\text{Ca}^+\text{Mg}^{2+}\text{-Y}$, the extent of exchange between Na^+ and Mg^{2+} or Ca^{2+} has to be higher than 54% to be detected in the supercages after water desorption at 400 °C (see Figure 1.4, left).^{6,20,21}

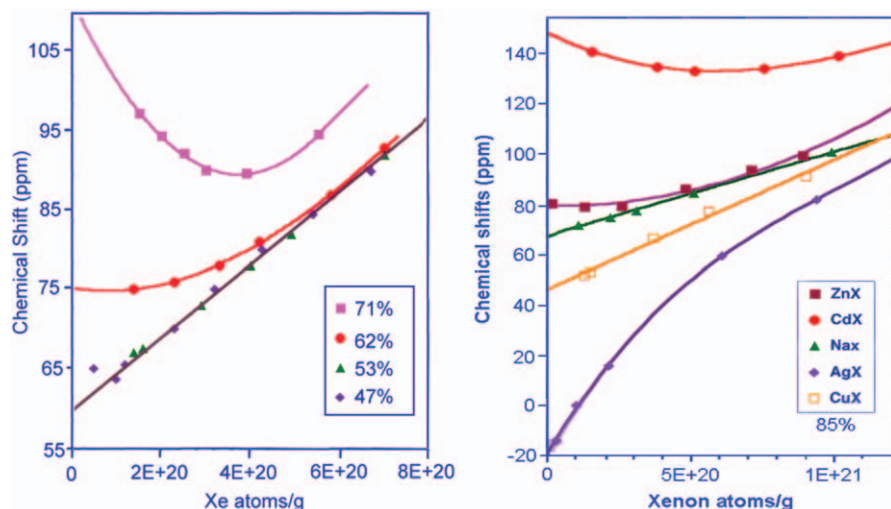


Figure 1.4 Chemical shift δ of adsorbed ^{129}Xe versus the number of Xenon atoms per gram of solid. Left: Na-Mg Y for various magnesium contents: $\blacklozenge$ 47%, $\blacktriangle$ 53%, $\bullet$ 62%, $\blacksquare$ 71%. Right: zeolites $\blacktriangle$ NaX, $\diamond$ AgX, $\bullet$ CdX, $\blacksquare$ ZnX, $\square$ CuX. (Reprinted from ref. 21, with permission of Elsevier.)

1.4.2 Cations with d^x Electronic Structure ($x > 0$)

When the cations have the nd^x electronic structure there is a competition between two opposed effects: the positive chemical shift due to the polarization of the xenon electron cloud by the charge of the cations; and a negative shift due to a nd^x-5d^0 donation from the cation to xenon during the short-lived cation-xenon complex. The resulting shift depends mainly on the charge of the cations, and also on their position in the pores. This effect is particularly important for $x=10$ such as Ag^+ , Cu^+ , Zn^{2+} and Cd^{2+} cations in faujasite-type structures (see Figure 1.4, right).²² For example the shift in Ag-X is distinctly lower than that for Na-X over the range of concentrations studied, exhibiting negative values in the range -40 to -50 ppm at low xenon concentration. The case of fully exchanged CuY or CuX zeolites is particularly interesting since the $\text{Cu}^{2+}\text{-Xe}$ and $\text{Cu}^+\text{-Xe}$ interactions give opposite upfield and downfield shift, respectively.²¹ This differentiation is important in view of the interest of Cu^+ in catalysis.

1.4.3 Other Charged Species

Xe NMR is particularly useful for the localization of La^{3+} , Ce^{3+} , Y^{3+} and Ru^{3+} cations in Y zeolite structure: supercages, hexagonal prisms or sodalite cages.²³⁻²⁵

Partially dealuminated zeolites often contain non-framework aluminium, Al_{NF} , in the pores and are generally detected by ^{27}Al NMR. Xe-NMR has

shown that the average charge on each Al_{NF} atom depends on the amount of Al_{NF} relative to the total number of Al atoms.^{26,27}

Finally we mention the interest in ^{131}Xe NMR of the 131 isotope for the quantification of the electric field gradient created by all charged species in zeolite pores.²⁸

1.5 Influence of Metal Particles Localized in Zeolite Pores

Metal–Xe interactions are much more important than Xe-surface interactions. At very low temperature δ_s characterizes the Pt particle size. In the case of fast exchange at 300 K, the spectrum depends on the size, the concentration and the distribution of the particles in the zones accessible to Xe.^{29,30} Finally, this technique makes it possible sometimes to demonstrate the bimetallic character of certain particles, as has been shown for Pt–Ir/Y based catalysts.³¹

1.6 Influence of Co-adsorbed Molecules. Zeolite Poisoning

Xe NMR is sensitive to the presence of a co-adsorbate; in particular to the type of its adsorption,³² shrinking core model³³ or non-uniform model.³⁴

Xe NMR is also a particularly interesting technique for the study of the chemisorption of gases on zeolite-supported metals. Indeed, the metal–xenon interaction depends greatly on the nature of the chemisorbed gas and the particle coverage by the gas, as well as the size and distribution of these particles in the zeolite.^{4,6}

Another application is the possibility to follow the poisoning of zeolites by chemical reactions; in particular, the deactivation of these solids by carbonaceous deposits (coke) during industrial cracking and their regeneration. In addition, Xe NMR is an efficient tool for locating coke inside or on the external surface of the zeolite. It can also reveal the role of extra-framework aluminium in catalytic cracking.⁴

1.7 Other Types of Microporous Solids

1.7.1 Clays

There have been several studies of pillared clays by Xe NMR; for example: montmorillonites pillared by cationic silicon species or by alumina, SiO_2 – TiO_2 sol, or hectorite pillared by tetraethylammonium ions. All authors obtained an average interlayer space in good agreement with XRD and porosity measurements. A more detailed review of these studies can be found in Gil *et al.*³⁵ The characterization of clays by ^{129}Xe NMR will be discussed in Chapter 9.

1.7.2 Heteropolyoxometalate Salts (HPOM)

Such compounds, used as selective oxidation catalysts, are ionic solids. The most common are those whose anions have the Keggin structure. Xe NMR revealed a microporosity resulting from a translation and/or a rotation of the Keggin anion in the crystal when the size of the cation increases.³⁶

Terskikh *et al.*³⁷ have shown that Xe NMR makes it possible to study silica-supported heteropolyacids and to follow the clustering of these molecules “step by step”.

1.7.3 Metal–Organic Frameworks (MOFs)

When the MOF structures are not affected by any adsorption or temperature variation the Xe NMR spectra show a monotonic increase in the chemical shift *versus* the xenon concentration which is typical for small pores in a rigid structure.^{38,39} But very often local structural changes of the MOF can be induced by chemisorption–desorption and/or by temperature variation. Adsorption of the xenon probe molecule was the first direct means of pointing out the structural flexibility of these materials. For example the MOF MIL-53 exhibits a structural transition between two possible pore structures, the so-called large-pore (lp) and narrow-pore (np) forms, depending on the temperature or when guest molecules are adsorbed.⁴⁰

The characterization of another MOF, Ni(2)(2,6-ndc)(2)(dabco), by gas adsorption and ¹²⁹Xe NMR reveals the reversible structural transformation of this compound without loss of crystallinity upon solvent removal and physisorption of several gases.¹²⁹Xe NMR seems to be the best technique for the detection and characterization of the so-called “gate-pressure” effect in this MOF material.⁴¹ The use of ¹²⁹Xe NMR for the characterization of MOFs is further described in Chapter 12.

1.7.4 Microporous Carbons

Besides the ordinary adsorption techniques, ¹²⁹Xe NMR is generally accepted for the characterization of zeolites, mesoporous and amorphous silica. In contrast, ¹²⁹Xe NMR has been only rarely used to study porous carbon materials. It has been mentioned in applications for the determination of the pore properties of activated carbons and coals,^{42–46} carbon black materials,^{47,48} various filamentous carbons including carbon nanotubes,^{49–53} polyacenic semiconductor materials⁵⁴ and graphitized carbon.² Most of these studies used experimental strategies derived from the ¹²⁹Xe NMR of more ordered porous solids. A few of them aimed at finding some specific ¹²⁹Xe NMR data for the characterization of the carbon surfaces.

In general, the ¹²⁹Xe NMR shift provides qualitative information and trends concerning the porosity and microstructure of amorphous carbons. However, in contrast to pure silicates, the interpretation of ¹²⁹Xe NMR data obtained for porous carbon is complicated by several factors: structural

disorder – distribution of the crystallite size or presence of amorphous domains; heterogeneity of surface properties – presence of various surface groups and surface structures (basal and edge); and conductivity and strong paramagnetic sites. The paramagnetic properties of porous carbon materials have several origins: structural defects naturally present in most of such materials and admixtures of paramagnetic particles of inorganic nature.

As a consequence, the relationships between δ_s and the pore dimensions of carbons were not found. Hence the idea of using another parameter to characterize the pore dimensions, one which is free of the direct solid-surface interaction. This parameter can only be the second virial coefficient, $\delta_{\text{Xe-Xe}}$, in eqn (1.1); this describes the interaction between xenon atoms in pores and, therefore, depends on the pore size and shape, which influence the xenon collision frequency. To overcome problems associated with the different types of carbons, Romanenko *et al.* prepared a series of activated carbons obtained by successive air oxidation/pyrolysis treatments of a unique precursor.⁴⁴ In this case, the chemical shift extrapolated to zero loading, δ_s , varies by 10 ppm over the pore size range 0.6–2.3 nm and without any monotonic behavior; this despite the fact that the chemical nature of the pore surface can be considered identical for all samples. Thus, δ_s cannot be used as a pore size probe. However, the chemical shift measured for these microporous carbons is a linear function of the xenon density, ρ_{Xe} , with a slope, $\delta_{\text{Xe-Xe}}$, which varies very linearly with the pore size according to the equation:

$$\delta_{\text{Xe-Xe}} = \eta + \kappa D \quad (1.7)$$

where $\delta_{\text{Xe-Xe}}$ is expressed in ppm cm³ mmol⁻¹; D is the mean pore size in nm, $\kappa = 7 \pm 0.2$ ppm cm³ mmol⁻¹ nm⁻¹ and $\eta = 5.1 \pm 0.3$ ppm cm³ mmol⁻¹.

Nevertheless, this equation cannot be generalized since there is no other study of microporous carbons with the same surface homogeneity.

Romanenko *et al.* have also used the term $\delta_{\text{Xe-Xe}}$ for the characterization of mesoporous carbons. In this case the number of Xe atoms in the pore volume, N_v , is negligible compared to the number of atoms on the surface, N_s . Thus, the collision frequency at the surface is much greater than that in the pore volume. Consideration of the chemical shift as a function of the surface Xe density, ρ_{surface} , is more logical. So eqn (1.8) is analogous to the eqn (1.1) for this case:

$$\delta(\rho_{\text{surface}}) = \delta_s + \delta_{\text{Xe-Xe(surface)}} \cdot \rho_{\text{surface}} \quad (1.8)$$

The coefficient $\delta_{\text{Xe-Xe}}$ was shown to increase with the mean pore size in the case of micropores.⁴⁴ In the case of mesopores, the opposite dynamic was reported.⁵⁰ A simple model describing these data has been proposed.⁵⁵

In another respect, carbon-supported metals are advantageous catalysts from an economic standpoint, since the metal recovery is rather easy. Indeed, the carbon support can be burnt off, leading to highly concentrated ashes.

As with zeolites, metal particles inside the pores or, on the contrary, on their external surface are easy to locate by Xe NMR.⁵⁶ An overview of these various applications has been published.⁵⁷

Finally, as with aluminosilicates, ^{129}Xe NMR is very useful for the characterization of micro-mesoporous carbons and the interconnection of the pores. For example, parallel studies with hyperpolarized ^{129}Xe of purely microporous carbon and mesoporous carbon, CMK-3, have unambiguously revealed the presence of micropores inside the CMK-3 structure.⁵⁸ In addition, ^{129}Xe 2D-exchange NMR experiments have clearly shown direct exchange of Xe atoms between the micro and the mesoporosity. This indicates the presence of micropores inside the carbon rods which make up the mesoporous structure of CMK-3 materials.

1.8 Conclusion

The ^{129}Xe -NMR of adsorbed xenon used as a probe is a very useful technique for the characterization of the properties of microporous solids such as zeolites, clays, metal-organic frameworks and even carbons. Indeed it is possible:

- to determine the dimensions and the form of their internal free volumes;
- to reveal and characterize the structure defects, and to calculate the short-range crystallinity, as opposed to that determined by X-rays;
- to locate cations in the zeolite structure and to define their interaction with adsorbed species;
- to characterize any encumbering species: adsorbed molecules, supported metal particles, coke formed during chemical reactions, *etc.*;
- to point out the structural flexibility of the metal-organic framework.

Acknowledgements

The author wants to thank Taro Ito from Sapporo who started with him on this long story and all members of the “Laboratoire de Chimie des Surfaces” of the University P. and M. Curie, Paris, who were his co-workers in this field during many years.

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CHAPTER 2

The Xenon Chemical Shift and Chemical Shift Anisotropy

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2.1 Scope and Emphasis

This review will focus on (a) understanding observed Xe chemical shifts at an electronic structural level and (b) using that level of understanding to deduce what the observed Xe chemical shift is telling us about the physical system of interest. The goal is to use the theoretical understanding of the observations in model systems in order to interpret more general Xe observations in complex systems, such as those mentioned in extensive reviews by Fraissard in this book and elsewhere. Hyperpolarized Xe uniquely permits the observation of the Xe chemical shift under conditions that are in the limit of no Xe–Xe interactions. Thus, we discuss “a single Xe atom” as a probe of physical systems separately. On the other hand, in observations of the Xe chemical shift under variable-loading thermally polarized Xe conditions, the anisotropy of the inner spaces becomes more obvious when Xe–Xe interactions dominate the intermolecular Xe shift tensor. We use first principles calculations to make predictions for static geometries and grand canonical Monte Carlo (GCMC) simulations and molecular dynamics (MD) simulations to do the averaging that makes possible predictions of a general nature and comparison with specific experimental observations. In this chapter we limit interpretation to systems which have well-characterized

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

structure and morphology, and observations in the slow exchange (with the gas) limit.

2.2 The Xe Chemical Shift under Conditions of Isotropic Averaging

2.2.1 The Xe Chemical Shift in Pure Xe Gas

The experimental temperature dependence of the density coefficient of the Xe chemical shift in Xe gas was established in 1970¹ after the pioneering work of Carr on the Xe resonance in the gas phase² showed how large the intermolecular effects on Xe chemical shifts in pure Xe could be,^{2,3} more than 300 ppm over a range of phases (solid, liquid, gas) and temperature.⁴ Using the formulation by Buckingham and Pople, the Xe chemical shift in the gas phase is expanded in a virial expansion in powers of density, just like the dielectric constant or other quantity for imperfect gases,⁵

$$\sigma(T, \rho) = \sigma_0(T) + \sigma_1(T)\rho + \sigma_2(T)\rho^2 + \sigma_3(T)\rho^3 + \dots \quad (2.1)$$

so that the second virial coefficient, the linear density coefficient of the Xe shielding in the limit of zero density, could be expressed exactly in terms of the Xe shielding as a function of Xe–Xe distance $\sigma(R)$ and the probability of finding a Xe atom at this distance,⁶

$$\sigma_1(T) = 4\pi R^2 \int_0^\infty R^2 dR \{ \sigma(R) - \sigma(\infty) \} e^{-V(R)/kT} \quad (2.2)$$

For Xe, σ_0 is the shielding for an isolated Xe atom which provides a convenient chemical shift reference, the limit of zero density. An accurate experimental determination of $\sigma_1(T)$ over a large enough temperature range could in principle permit the direct inversion of the data to yield the Xe–Xe intermolecular shielding function $\sigma(R)$, using an accurately known Xe–Xe intermolecular potential function, as we suggested in 1975,⁷ but the limited temperature range could only result in an estimated form.

2.2.1.1 The Intermolecular Shielding as a Function of Distance and Angle in Xe₂ and in Xe₃

The characteristics of the intermolecular shielding function $[\sigma(R) - \sigma(\infty)]$ for Xe–Xe interaction, $\parallel$ and $\perp$ components, have been established.⁸ Relative to the isolated Xe atom, the $\parallel$ component in Xe₂ is only a small shielding increment, whereas the $\perp$ component is a large deshielding response changing very steeply with close approach. The shape of the intermolecular shielding function $[\sigma(R) - \sigma(\infty)]$ was first estimated using a direct inversion of the experimental temperature-dependent density coefficient of shielding.⁷ On this basis, the characteristic shape of the intermolecular shielding function was suggested in conference talks by the author in late 1970s, and

was first calculated *ab initio* in 1992 for the Ar–Ar model at the RHF level.⁹ Scaling these results provided the first *ab initio*-based calculations of $\sigma_1(T)$ for Xe–rare gas pairs and also the first exploration of the additivity of intermolecular shielding, using the Ar₃ cluster. The intermolecular shielding tensor calculations for Xe₂ dimer were later carried out at the RHF level, using 240 basis functions for Xe.¹⁰ This basis set was originally used by Bishop to calculate the shielding response to an electric field and has become the standard one to use for Xe shielding calculations. Electron correlation contributions were later included, also for Xe–other rare gas systems using DFT-B3LYP.⁸ Later refinements of electron correlation contributions by Vaara *et al.*¹¹ showed that CCSD theory can be regarded as a reliable and nearly converged electron correlation method for calculating the NMR shielding in Xe₂, at the non-relativistic level,¹¹ and after adding relativistic contributions (about 8%),¹² the experimental temperature dependence of the second virial coefficient of ¹²⁹Xe shielding is reproduced better than ever before.

The characteristics of the shielding tensor surfaces as a function of angle and $R(\text{Xe–Xe})$ in the Xe₃ cluster establish the limits of the pairwise additivity of Xe–other shieldings.¹⁰ Subsequent non-relativistic RHF calculations by Vaara *et al.* also show that pairwise additivity of Xe shielding holds for most interatomic distances for Xe_{*n*} clusters ($n = 3–12$).¹³ Further discussion of the pairwise additivity and its limits are in Section 2.3.1.1.

2.2.1.2 Beyond the Binary Interaction Limit. The Sign of Higher Order Terms

Since *ab initio* calculations show that the deviations from pairwise additivity of intermolecular Xe shielding become significant only at very short distances, then using pairwise additive shielding functions together with pairwise additive intermolecular potential energy functions can lead to semi-quantitative predictions of experimental Xe chemical shifts *except* at conditions of extremely high Xe densities. In eqn (2.1) the sign of $\sigma_2(T)\rho^2 + \sigma_3(T)\rho^3 + \dots$ was found to be opposite to that of $\sigma_1(T)\rho$ in pure xenon gas for Xe number densities 100–250 times that of an ideal gas at standard conditions.¹ It has been found to be uniformly true for other nuclei, as well that the magnitude of the *effective* density coefficient at liquid densities:

$$\frac{[\sigma - \sigma_0(T)]}{\rho(T)} = \sigma_{1,\text{effective}}(T) \quad (2.3)$$

is smaller than that of the density coefficient in the limit of vanishing density in the gas.¹⁴ For much higher densities, there are two quantities that are different from eqn (2.2): the shielding function itself is no longer strictly a pair function, that is, it depends on the cooperative shielding response to many atoms at a time and is a function of their configuration. Second, the probability of finding a neighbor atom is no longer given by the dilute gas

limit form of $\exp[-U(R)/kT]$. The density dependence of the Xe chemical shift measured in supercritical xenon up to nearly 500 times the density of an ideal gas at standard conditions^{15,16} is in complete agreement with this.

2.2.2 The Chemical Shift of the Single Xe Atom as a Probe of the Physical System

The Xe chemical shift has been found to have many applications in the characterization of materials, including biological systems. Understanding the chemical shifts helps us to make predictions in systems beyond those where measurements have been carried out. We introduce complexity in steps. In this section we consider examples of Xe chemical shifts as a probe of the physical system in the limit of no Xe–Xe contributions and under conditions of isotropic averaging. In Section 2.3.1 we consider the chemical shift tensor of a Xe atom in anisotropic spaces in the solid state and in 2.3.2 we consider probing physical systems with Xe–Xe contributions to the shift tensor.

2.2.2.1 The Xe Atom in a Homogeneous Electric Field

Electric field contributions have often been mentioned as a significant contribution to Xe chemical shifts in zeolites and other systems where charged species may be present. To be precise, the effects of electric fields on the Xe atom response to a magnetic field is actually small. For a homogeneous electric field E ,

$$\sigma(E) = \sigma(\text{isolated, field-free Xe atom}) + BE^2 \quad (2.4)$$

where the quadratic electric field coefficient of shielding, $B = (1/3)[(1/2)\sigma_{zzzz}^{(2)} + \sigma_{zzxx}^{(2)}]$.¹⁷ *Ab initio* non-relativistic MP2 calculations yield $B = 4404$ ppm au¹⁸ vs. 2415 ppm au from more recent 4-component relativistic calculations.¹⁹ These values of B lead to very small chemical shifts for Xe. Effects of electric field gradients on Xe shielding are likewise small.²⁰ Therefore, electrostatic effects on Xe shielding from bare charges are almost insignificant. For example, when a Xe atom shielding is calculated in the presence of a lattice of point charges representing H and O atoms in crystalline clathrate hydrates with a Xe basis set constituted to provide quantitative electric field response, the Xe chemical shift is found to be of the order of only a few tenths of a ppm.²¹ Differences in Xe chemical shifts commonly attributed to ‘electric field effects’ actually come from the response of the electrons of Xe to the changes in the electronic structure of the lattice atoms (typically O atoms) when a framework Si atom is replaced by an Al atom plus a charge-balancing positive ion, for example. Although the Xe shielding response is a local property in that it comes from Xe electrons experiencing overlap, exchange and correlation with electrons of an immediate neighbor, any changes in the electronic structure of the neighbors arising from long range

effects will show up in the Xe shielding response. It is for this reason that Xe is such an exquisite probe of its environment.

2.2.2.2 The Xe Atom in a Gas Mixture

The Xe shielding tensor surfaces for Xe-Rg (Rg = Xe, Kr, Ar, Ne) provide models for the dependence of Xe intermolecular shielding on the electronic structure of the atom eliciting the Xe response.⁸ Qualitatively the magnitude of the response is greater for Rg with greater polarizability.

Ab initio calculations of nuclear shielding surfaces [$\sigma(R, \Omega) - \sigma(\infty)$] have been carried out for Xe interacting with molecular partners such as N₂, CO₂, CO,^{22,23} O₂,²⁴ CH₄ and CF₄.²³ The shielding surfaces could be mathematically represented by sums over Xe-C and Xe-H contributions for Xe-CH₄, and by Xe-C and Xe-F contributions for Xe-CF₄ fitted to regenerate the large number of *ab initio* values calculated at a large number of configurations (*ca.* 100). Using this form of mathematical representation of the *ab initio* shielding values permits the Xe-C and Xe-H functions to be used later to estimate Xe shielding in liquid solvents, *e.g.*, Xe-alkane systems, and Xe-C and Xe-F functions to estimate Xe shielding in Xe-perfluoroalkane systems. For accurate calculations to reproduce the $\sigma_1(T)$ that result from experimental data obtained in the gas phase in the binary collision limit, it is very important to use accurate intermolecular potential functions that properly weight the calculated shielding functions, especially at short distances where the shielding changes very steeply. Furthermore, the shielding functions are highly θ -dependent, thus we need the correct θ dependence of r_0 of the intermolecular potential in order to obtain accurate density coefficients in the gas phase. Gas phase NMR data prove to be stringent tests of calculations, much more so than condensed phase. Pressure virial coefficients do not provide adequate tests for intermolecular potential functions. Piecewise functions parameterized to multiple experiments of high precision, including detailed scattering data from crossed molecular beam experiments, are found to be necessary for empirical-based potentials. On the other hand, *ab initio* surfaces calculated at the CCSD(T) level have been found to give results comparable to the best empirical-based potentials, see for example, $V(\text{Xe-Xe})$ calculated by Vaara *et al.*¹¹ Thermophysical properties which are used for empirical determinations of intermolecular potential functions are usually sensitive to the volume of the attractive bowl, but shielding averages need more accurate R dependence of the potential energy at short range. Classical MD simulations often use Lennard-Jones forms for non-bonded interactions; these L-J forms usually give inappropriate weighting of the shielding at close approaches. Thus, we recommend potential functions of the Maitland-Smith form, suitable for Monte Carlo simulations, and exp-6 form suitable for MD simulations.

Xe chemical shifts in the presence of O₂ or other paramagnetic molecule requires not only the calculation of the usual magnetic shielding response but also the hyperfine tensor as a function of configuration.²⁴ For the density

and temperature dependence of the Xe chemical shift in O₂ gas,²⁵ only the isotropic part of the hyperfine tensor, the Fermi contact part, can contribute since the traceless dipolar part averages isotropically to zero in the gas phase. On the other hand, the traceless dipolar part is responsible for the electron-spin-dipole–nuclear-spin-dipole mechanism for the relaxation of ¹²⁹Xe nuclear spin in the gas phase mixtures containing O₂, which we have also measured.²⁶

2.2.2.3 The Xe Atom in Solution

The first observations of Xe chemical shifts in solution were made by Stengle and Williamson,^{27–29} and they interpreted their results using reaction field theory. Experimental data are usually in the limit of Xe infinitely dilute in the liquid solvent, no Xe–Xe contributions. As we have seen above, dilute gas phase observations can be reproduced by direct integration of intermolecular shielding functions using the intermolecular potential function. For the Xe atom in a solvent, this type of averaging is no longer possible because of the many-body interactions in both the shielding response functions and in the potential energies associated with the system configurations. As a consequence, even in the limit of highly accurate *ab initio* calculations of the intermolecular shielding response in interacting molecular systems, the averaging can no longer be carried out to high accuracy. There are simply too many assumptions which can lead to error. Often by necessity, empirical “force fields” are used to define the nature of the liquid structure. With this caveat, we consider several methods of averaging Xe chemical shifts for Xe in liquid solvents such as to include temperature and dynamic effects.

First we consider general approaches to dynamic averaging of Xe shielding in condensed phases. Xe intermolecular shielding drops off with distance so that electronic structure of only those atoms within 6–10 Å of the Xe need to be accurate for Xe shielding hypersurface calculations. However, long range effects can contribute indirectly by affecting the electronic structure of the atoms nearest to Xe and also by affecting the distribution of those atoms in space, *i.e.*, the “free volume” in which the Xe atom executes its dynamics within the solvent cage, within an ionic liquid channel, in a protein pocket, or a transient pocket within a glassy polymer. Therefore, accurate description of the physical system, including theoretically difficult long range effects, is needed. As *quid pro quo*, it is precisely these effects that make Xe chemical shifts exquisitely sensitive to the environment; even when we are unable to describe the environments accurately quantum mechanically and classically, the distinct Xe chemical shifts in only slightly different environments serve as a sensitive and useful diagnostic property. The dependence of Xe chemical shifts on local geometry is revealed in variable temperature measurements. Any interpretation of Xe in condensed phase materials must be tested against the experimental temperature dependence of the Xe chemical shift since dynamic simulations at various temperatures

require no change in the parameters of the shielding or potential energy surfaces. The dynamic averaging may be carried out in various ways, but, in general, one needs a means of generating configurations over which the averages are taken and a means of generating the shielding for a given configuration.

The means of generating configurations may be *via* a Monte Carlo (MC) process for canonical or grand canonical ensembles or *via* a (classical or quantum) molecular dynamics (MD) trajectory. Both methods of generating configurations have been used for dynamic averaging of Xe shielding. The usefulness of MD simulations is limited by their short duration. The shielding calculation converges quickly, but if the MD is to produce the correct long range structure of the physical system (which we need for accurate Xe intermolecular shielding for reasons discussed above), the pre-equilibration MD has to be done over a long enough trajectory or start from a configuration very close to the actual equilibrium configuration, or else various techniques such as simulated annealing have to be employed to let the system get over barriers in the potential energy hypersurface. In classical MD, the interaction potentials between the particles are functions of the inter-particle coordinates and may include pairwise, three-body, and higher order terms, whose functional forms are related to the nature of interactions and bonding in the system under study. These parameterized functional forms have been obtained by fitting the parameters to a set of experimental or theoretically calculated data. Many widely used combinations of potentials (or force fields) specifically developed for biological systems (AMBER, CHARMM, GROMOS, *etc.*) or systems consisting of organic molecules (OPLS) have been used extensively in dynamic averaging of shielding of various nuclei in solutions. Beyond classical MD are quantum MD methods which have been used for shielding calculations for other nuclei³⁰ but not for Xe shielding. The biggest weakness in using classical MC or MD simulations arises from the intermolecular potential functions used in the simulations. It is therefore important that these be tested independently by reproducing other physical quantities such as adsorption isotherms or solubility, or else quantum MD such as CPMD, which calculates all interactions quantum mechanically, should be used.

There are various means of generating the Xe shielding for a given configuration. Obviously, this is based ultimately on quantum mechanical calculations of Xe shielding. For the purpose of dynamic averaging, shielding may be calculated using Periodic Boundary Condition (PBC) methods for a completely QM description of the entire system as represented by a supercell.³⁰ In principle PBC methods could be applied to Xe shielding in a crystalline or amorphous polymer, or to a Xe shielding in a protein pocket. In an alternative approach, only a finite number of molecules are included in a cluster, the molecule in question plus some number of neighbours. The cluster method has been used for a rare gas atom in a zeolite cage³¹ or an organic cage,^{32–35} or a pair of molecules at various distances and orientations.^{8,23,24} The number of molecules in the cluster could be two or

more; for example, calculations of the shielding for Xe in benzene have included 9–10 benzene molecules in the cluster,³⁶ and the calculations for Xe in clathrate hydrates included 40–48 explicit water molecules.²¹ An improvement is afforded by an embedded cluster approach. The cluster may be placed in a reaction field, or the cluster may be embedded in a collection of self-consistently determined point charges while doing the quantum calculation,²¹ using embedded ion EIM³⁷ or enhanced embedded ion EEIM³⁸ methods to determine the charge field that describes the periodic lattice.

Finally, the procedure for doing the averaging of the intermolecular shielding is, in general, (a) to select a series of configurations from MD or MC simulations, do quantum calculations of shielding for those snapshots and take the equally weighted average, or (b) to use pre-calculated shielding hypersurfaces and evaluate the average during the process of generating the configurations in an MD or MC simulation. We cite some examples in the following.

2.2.2.3.1 Quantum Calculations of Shielding from MD or MC Snapshots.

This is a commonly applied method of averaging in condensed phase. In this method, the snapshots are first generated and then the shielding calculation is done for each snapshot. For Xe in benzene solution, the highly anisotropic nature of the interaction between Xe and the benzene molecule makes it difficult to precisely express the set of calculated shielding values for Xe at various positions relative to a benzene molecule into a suitable analytic mathematical form of the Xe shielding hypersurface. Instead, Standara *et al.*³⁶ carried out classical MD simulations of one Xe atom in a periodic box of benzene molecules and selected snapshots from the classical MD trajectory. A cluster including a Xe atom with its first solvation shell of 9–10 benzenes was carved out of each selected snapshot. This cluster was used for the quantum mechanical calculation of the isotropic ¹²⁹Xe shielding using non-relativistic density functional theory as well as relativistic Breit–Pauli perturbation corrections. Thus, the correlation and relativistic effects as well as the temperature and dynamics effects could be included in the calculations.³⁶ Most of the experimentally observed isotropic ¹²⁹Xe shift was recovered in the nonrelativistic dynamical region, while the relativistic effects explain about 8% of the total ¹²⁹Xe chemical shift. Theoretical results are found to agree with the experimental value at room temperature. This was a rather fortunate result, since the Xe–benzene potentials used were approximate, taken from mixing rules and Xe L–J potentials ($r_0 = 3.975$ Å, $\epsilon/k = 214.7$ K) and not previously tested against the equilibrium structure and optical spectra of Xe–benzene van der Waals complex, for example, or other appropriate experimental data.

2.2.2.3.2 Use of Pre-calculated Shielding Hypersurfaces in MD or MC Simulations. For Xe in liquid water, *ab initio* calculations of Xe shielding surfaces were carried out (as a function of position within the cage) in the

rigid experimental geometry of various clathrate hydrates of known neutron diffraction structure with disorder in the proton positions constrained to follow the ice rules, including the effects of the extended lattice in the *ab initio* calculations; then the *ab initio* shielding tensors were mathematically expressed in terms of pairwise Xe–O and Xe–H terms, which are functions of distance. Monte Carlo simulations of Xe chemical shift tensors in the various clathrates had been used to verify the Xe–H and Xe–O shielding functions against Xe@clathrate spectral lineshapes. The pre-calculated isotropic Xe–H, Xe–O shielding functions in rigid solvent cages in the extended lattice system were used as the shielding functions for Xe in liquid water, calculating the Xe shielding contributions on the fly during the MD trajectories in simulations of Xe solution in liquid water.³⁹ A well-established liquid water potential and the same Xe–H and Xe–O interaction energy functions used for Xe in the clathrate hydrates were used to calculate the Xe–H and Xe–O interactions. Results are in excellent agreement with experimental Xe chemical shift in liquid water, not surprising since the shielding functions had been tested against the solid state experiments in clathrate hydrates, reproducing not only the isotropic shieldings but the anisotropic line shapes as well.

There are data for Xe in liquid N₂,⁴⁰ and Xe in liquid CO₂ and liquid NNO.⁴¹ Although the shielding functions have been calculated for these Xe-linear molecule pairs using DFT methods, these shielding calculations and/or the established intermolecular interaction potentials were not accurate enough when tested against the gas phase density coefficients of Xe chemical shift as a function of temperature; only semiquantitative agreement with experiment was found.²³ Nevertheless the methods are now well known and *ab initio* calculations using CCSD(T) with perturbative relativistic corrections for Xe shielding at various (*R*, Ω) configurations can be carried out. With large enough basis sets, *ab initio* CCSD(T) calculations of the Xe-linear molecule intermolecular interaction potentials could yield as good a quality as was found for the best empirical Xe–Xe potentials.¹² The isotropic Xe chemical shift as a function of temperature for Xe in liquid N₂, and supercritical CO₂ and NNO can then be calculated.

There exists a large amount of data for Xe chemical shifts in liquid alkanes in various homologous series.^{42–45} In that literature, the global interpretation of the Xe chemical shifts in terms of constitutive contributions of CH₃ and CH₂ groups and corrections for cyclic *vs.* normal chains had been incorrect and counter-intuitive, primarily because of making comparisons of Xe chemical shifts in liquids at the same temperature, as opposed to comparing them in liquids at the same thermodynamic state. Another empirical assignment of group contributions had been attempted.⁴⁶ A rational comparison of Xe chemical shifts in different solvents in a homologous series can be made if the solvents are in the same thermodynamic state. This was brought to the attention of the Xenon NMR community by E. J. M. Felipe and R. Bonifacio at the first XeMAT conference in 2000. They suggested using liquids at the same reduced temperature (T/T_c) or reduced density (ρ/ρ_c).⁴⁷

They have since carried out simulations of Xe in the various liquid solvents illustrating this concept.⁴⁸ We carried out atomistic MD simulations of Xe in normal alkanes and cyclo-alkanes using pre-calculated Xe shielding hyper-surface for Xe-CH₄, fitted to pairwise sum of Xe-C and Xe-H functions and tested against the temperature dependent density coefficient of Xe chemical shift in CH₄ gas. These functions are used to calculate Xe shielding on the fly during the MD trajectory; using a cutoff distance and periodic boundary conditions permits simulations to be carried out for the entire solution. Since the additive chemical shift contributions from the CH₃ and CH₂ groups are obtained separately in the simulation, we determine these constitutive contributions to the Xe chemical shift for each temperature in each solvent and find that per CH₃ contributions are greater than per CH₂ contributions for each case, a ratio of around 1.5. One of the possible physical insights to be drawn from the above comparisons is the effect of the accessibility of the functional group in the solvent molecule on its contribution to $\sigma_{1,\text{effective}}(\text{Xe-solvent})$ in eqn (2.3). For example, end groups have a distinct advantage in contributing to the Xe chemical shift because of the site effect. This means that the CH₃ group contribution to the effective second virial coefficient of the Xe chemical shift in the solvent should be larger than CH₂, not only because there are more atoms contributing to the sum of Xe responses, but also because of the site effect. At the same reduced temperature, $(T/T_c) = 0.5$, the CH₃ (and the CH₂) contributions to $\sigma_{1,\text{effective}}(\text{Xe-solvent})$ are nearly constant and therefore can be considered transferable from one alkane to another. This permits the prediction of the Xe chemical shift in higher alkanes ($n = 9-16$) from their experimental density, using the CH₃ and CH₂ contributions from MD in alkanes ($n = 4-8$).⁴⁹ The values of $\sigma_{1,\text{effective}}(\text{Xe-CH}_2)$, the per CH₂ contribution at $(T/T_c) = 0.5$ are found to be very similar for the $n = 5, 6, 8$ cyclo-alkanes ($\sim 2.69 \text{ ppm mol}^{-1} \text{ L}^{-1}$ per CH₂) found in MD simulations but smaller than the corresponding values ($\sim 3.14 \text{ ppm mol}^{-1} \text{ L}^{-1}$ per CH₂) found in the linear alkanes.⁵⁰ The site effect, the CH₂ in linear alkanes are more accessible to Xe than the CH₂ in cyclo-alkanes, is obvious here. The additive nature of Xe intermolecular shielding lends itself to sensible constitutive contributions for Xe chemical shifts in homologous series of solvents.

A particularly interesting Xe chemical shift is that for Xe in the blood substitute PFOB (perfluorooctylbromide).⁵¹ Using the same MD method, the Xe chemical shifts for Xe dissolved in water (as described above) and Xe dissolved in PFOB were individually accurately predicted,³⁹ respectively 105 ± 5 and 195 ± 5 ppm relative to the isolated Xe atom, to be compared with the experimental 106 and 196 ppm. The Xe in PFOB was calculated by MD simulations carried out using the additive Xe-C, Xe-F and Xe-Br shielding functions. The Xe-C and Xe-F shielding functions were taken from the *ab initio* calculations in the Xe-CF₄ dimer system at various configurations, represented by fitting to pairwise Xe-C and Xe-F shielding functions of distance only, tested against the experimental Xe chemical shift in CF₄ density coefficient as a function of temperature in the gas phase.²³

The Xe–Br shielding function was obtained from the Xe–F shielding function by well-established shielding scaling factors for atoms in the same family in the Periodic Table.⁹ These studies of Xe in liquids lead to the following general conclusions: the Xe chemical shift in liquid solutions depend on the local contributions to the Xe shielding by atoms or groups of atoms. Therefore, the Xe chemical shift in a solution is determined by the chemical constitution of the solvent molecule and the accessibility of the Xe to the various atomic groups in the solvent cage, the same quantities which determine Xe shifts for xenon in gas mixtures and xenon trapped in solid structures. Changes in temperature affect the distribution of the atoms or groups of atoms of the solvent relative to the Xe position. In dilute gases, this is governed by $\exp[-V(R,\Omega)/kT]$. In solutions, the structure of the liquid changes with the thermodynamic state, the density typically decreasing with increasing temperature, leading to smaller Xe chemical shifts. What can be compared from one liquid solvent to another are the density coefficients at the same reduced temperature, the Xe-group contributions to the density coefficients being about the same as long as their accessibility to Xe is about the same.

Ionic liquids (IL) have more local structure than ordinary liquids.⁵² One of the most important features of ionic liquid structure is charge ordering, the need to maintain a lattice-like arrangement of cations and anions to minimize the Coulombic energy of the liquid.⁵³ It has been estimated that the size of local structures is several tens of nanometres.⁵⁴ This is consistent with the fact that some ionic liquids experience unusually long equilibration times.⁵⁵ A typical ionic liquid is 1-alkyl-3-methylimidazolium cation and a selected anion. The crystal structure of 1-butyl-3-methylimidazolium chloride shows channels in which the Cl^- anions are accommodated as chains.⁵⁶ The close contact (2.5–2.7 Å) between three H atoms of the cation and the Cl^- ion indicate hydrogen bonding and the out-of-plane all-*trans* configuration of the *n*-butyl group is probably the reason for the large separation distance between the two imidazolium rings. There is spectroscopic evidence (Raman) that the local structure in the liquid is very similar to that in the crystal. Xe chemical shifts of xenon dissolved in 1-alkyl-3-methylimidazolium ionic liquids are large, ranging from a low of 161.1 ppm for the bulky anion bis(trifluoromethanesulfonyl)imide to 215.5, 228.5, 253.5 ppm for Cl^- , Br^- , and I^- , respectively, relative to the low density gas.⁵⁷ These measured shifts appear to have negligible Xe–Xe contributions. These results and an additional set of ^{129}Xe chemical shift measurements of Xe dissolved in four IL homologous series based on 1-alkyl-3-methylimidazolium cations, $[\text{C}_n\text{mim}]^+$, $n = 2\text{--}12$, combined with different anions, (altogether 30 distinct ionic liquids) were interpreted by Filipe *et al.* using MD simulations.⁵⁸ Comparing these various ionic liquids at the same thermodynamic state is easier than with alkanes; at room temperature all are at approximately the same reduced temperature $T/T_c \sim 0.25$. The MD simulations provide the $g(r)$ Xe–A radial pair distribution functions, where A = imidazolium ring, or anion, or various carbons of the alkyl side chain. To obtain the Xe–A

contribution to the chemical shift, it would be necessary to integrate the Xe–A shielding function of $R(\text{Xe–A})$ weighted by the $g(r)$ for $r \sim 0.75r_0$ to $r = \text{cut-off}$, which in this case was 16 Å. It would have been interesting to see the one-body distribution function for Xe in the ionic liquids, which could easily have been collected during the MD. The one-body distribution function would give a better picture of where the Xe spends most of its time. With progressively longer alkyl chains, the Xe tends to “disappear” from the vicinity of the imidazolium ring and have a greater probability of being found near the terminal group (CH_3) of the alkyl chain.⁵⁸ This would counter the speculations in the previous work by Castiglione *et al.*⁵⁷ which explained the observed Xe chemical shifts for ILs with different anions by guessing the volume of the “cavity” where Xe might reside.

Xe is such a sensitive probe of liquid structure that it can detect the presence of ions in solution⁵⁹ or changes in hydrogen bonding structure of the liquid due to deuteration.⁶⁰

2.2.2.4 Xe Atom in a Cage in Solution

We have seen that Xe shielding response is steeply changing at short distances and that the Xe chemical shifts in solution depend on the average internal volume of the solvent cage, the “free volume” in the liquid solvent which changes with temperature. A stringent test of this idea is the Xe shielding in a semi-rigid cage of known structure, *e.g.*, C_{60} . The fullerene C_{60} has been synthesized such as to encapsulate a Xe atom. The Xe chemical shift has been measured, 182.35 ppm when expressed relative to Xe atom.⁶¹ It is to be expected that RHF calculations cannot fully describe the shielding response provided by C_{60} which itself requires electron correlation to reproduce its equilibrium geometry. DFT-B3LYP-optimized geometry was very close to experimental geometry, and DFT calculations using B3LYP functional could provide a Xe chemical shift in reasonable agreement with experiment. It was found in this study that the Xe shielding is very sensitive to the geometry of the cage as defined by the C–C bond lengths.³² Single point calculation of Xe shielding at the center of the cage provides a chemical shift of $[\sigma(\text{Xe atom}) - \sigma(\text{Xe}@C_{60})] = 181.6$ ppm, fortuitously close to experiment; indeed the B3LYP functional has been found to overestimate Xe chemical shifts in general. Because of the tight fit of Xe in this cage, the dynamic average over various Xe positions within a rigid cage is expected to be small and was later found to be no more than 0.5 ppm.⁶² More recent calculations using the BH and HLYP functional and molecular mechanics geometry for the cage found the non-relativistic value for $\text{Xe}@C_{60}$ at rest in vacuum is only 132.1 ppm.³³ Relativistic corrections using Breit–Pauli perturbation theory for this condition is 14.2 ppm. The dynamic effects from thermal averaging of the C_{60} geometry, and the effect of benzene solvent, which had been thought to be small, was later found to be of the order of 14.1 and 12.3 ppm.³³ Unfortunately, there are no measurements of the temperature dependence studies of the Xe chemical shift in this system to check these

estimates, and the MD of the C_{60} cage in benzene solvent used empirical potentials which could lead to a C_{60} cage which is too flexible.

There is no exchange of Xe between the inside and outside in this case; the C_{60} has to be chemically opened to permit this. A series of cages which do permit a slow exchange of Xe, slow enough for measurement of Xe chemical shift inside the cage, is the cryptophane series which have two cyclo-tribenzylene caps joined by three linkers, where the linkers are $-O-(CH_2)_n-O-$.⁶³ Cryptophanes are the best molecular hosts for Xe when the linkers are relatively short. Xe has been trapped in cryptophane A (222), where each of the three linkers are $-O-(CH_2)_2-O-$,⁶⁴ and in cryptophane 223 and 233,⁶⁵ in cryptophane 333,⁶⁶ and in cryptophane 111.⁶⁷ We mapped out the Xe shielding in various locations within the cryptophane A (222) cage³⁴ by doing DFT-B3LYP and RHF calculations; RHF results were insufficiently deshielding, while B3LYP-DFT results were too deshielding. This is a rather general result for Xe shielding calculations using DFT. We fitted the shielding values to pairwise additive Xe-A shielding contributions, each a function of distance, where site A differentiates between three types of carbons: ring, CH_2 in the cap, C-O in the OCH_2CH_2O linkers or the OCH_3 , and each oxygen atom is represented by a site at the oxygen center and a site representing the centroid of the lone pairs 1.2 Å from the oxygen center. Using these Xe-site shielding functions, the quantum mechanical values of the Xe shielding at various Xe positions in the cage could be reconstituted. All the Xe-A functions were monotonically deshielding with decreasing distance except for Xe- C_{ring} . *Ab initio* values were positive in a small region where ring currents would predict shielding rather than deshielding. These findings would lead to predictions of unusually small Xe chemical shifts in cryptophane 111, where the linkers are short, thereby forcing the Xe to spend more time in those positive regions in comparison with the cryptophane 222, or 223 or 233. Indeed it is found experimentally that in 111, the volume inside the cage may be smaller, yet the average Xe chemical shift is not greater than in 222.⁶⁷

The general trends of Xe chemical shifts with cage size, when comparing similarly constituted cavities, arise from the universal shape of the Xe shielding response function proposed by us in 1982 and verified by *ab initio* calculations on Ar and later on Xe.^{8,9} The dependence of the Xe chemical shift on cage size follows from the fact that a smaller cage provides the Xe atom with many more atoms at short distances to evoke a large quantum mechanical shielding response. More polarizable atoms evoke a larger Xe shielding response. Care should be exercised when the constitution of the cage is such that some chemical groups are sampled more than others, or in the case of highly anisotropic groups. In liquid benzene, Xe samples all positions in plane and out of plane, above the ring and so on. In a cryptophane cage, Xe can only sample the benzylenes groups above the plane and only in certain regions relative to the ring, thus the averaging is very different, weighing only some regions and not others because of Xe confinement in the cage. A more subtle example of dependence on cage size

is the differential Xe chemical shifts upon successive deuteration of the cage.⁶⁸ Our interpretation is that the heavier deuterium mass does not permit the larger vibrational excursions of the lighter proton, leading to small incremental shifts with each D replacement. Simply making the r_0 of the Xe–D potential function 0.07 Å shorter than that for Xe–H, while keeping all other quantities the same, is sufficient to provide the observed differential shifts upon D substitution at the linker and the methoxy groups. The per-D isotope effect being smaller for the methoxy than the linker is reproduced, showing that our MD simulations of Xe atom in the cage predicts the correct relative accessibility of linker *vs.* methoxy groups.

Derivatives of cryptophane A (CryA) have been synthesized for the purpose of using the Xe in the cage as a biosensor, by attaching a biological ligand. The initial publication on xenon biosensors by the Pines group suggested the possibility of multiplexing, that is, using several cage types or derivatives with different biological ligands to detect several targets at the same time.⁶⁶ This concept is based on the Xe chemical shifts being tuned to different points on the Xe chemical shift range by choice of substituents or using more than one cage architecture. The mechanism of the sensing action, *i.e.*, a different Xe chemical shift for the free sensor molecule than the sensor molecule attached to the target, has been established to be due to the dynamic average for the Xe in cage in the free sensor molecule being different than when the sensor is attached to the target.³⁴ The cage undergoes different molecular dynamics in the attached sensor because contact of the cage with the protein surface leads to greater deformations of the cage than for the free-floating sensor. From the calculations it was predicted that the shorter the tether, the larger is the Xe chemical shift difference between the attached and free sensor. This trend was later observed when biosensors with varying tether lengths were synthesized.⁶⁹ The cryptophane cage itself is handed and is commonly synthesized as a racemic mixture. When an attached ligand is achiral, the NMR signal of the Xe atom in the functionalized cage in solution is a single isotropic peak, since the Xe shielding tensor components in the **R** and **L** cages differ by no more than the signs of the off-diagonal elements. Chiral substituents can split the cage-encapsulated Xe NMR signal into one or more sets of doublets, depending on the number of asymmetric centers in the substituent. The Xe chemical shift discriminates between diastereomers, leading to splitting of signals.³⁵ The dynamic interactions between the tether and the cage are different for the various handed tethers: In a sense, the left handed tether arranges itself around the left-handed cage differently than on the right-handed cage. The electronic structure of the cage can detect this difference and, in turn, the Xe can detect the difference in the cage shielding response. A combination of *ab initio* calculations and molecular dynamics simulations have permitted us to assign the observed split peaks to the **RI** and **LI** diastereomers. Where the substituent itself possesses two chiral centers, calculations permit the prediction of the Xe spectrum of diastereomeric systems in solutions containing **Llr**, **Rlr**, **LlI**, and **RII** systems.³⁵

Other groups have synthesized variants of the Xe@CryA biosensor. When the substitution is for the CH₃ group in one of the –O–CH₃ moieties in CryA, Xe in the functionalized cage is more shielded (smaller chemical shift relative to Xe atom) in the original Pines *et al.* biosensor⁶⁶ than in the parent cage, as our calculations predicted,³⁴ and this too has been found to be the case in other variants.⁷⁰ The sensing mechanism for the new protein sensors^{71,72} appears to be the same as we proposed earlier, deformation of the cage upon binding of the sensor to the protein, leading to higher Xe chemical shift in the bound than the unbound sensor. On the other hand, the sensing mechanism for detecting a specific DNA target, which has the Xe in a cryptophane A covalently attached to a spacer attached to a single strand of the complementary nucleotides, is different; association between sensor and target toward the formation of the double stranded DNA causes the encapsulated Xe to move to 1 ppm lower chemical shift.⁷³ The criteria required for an efficient biosensor have been reviewed comprehensively.⁷⁴

2.3 The Intermolecular Xe Chemical Shift Tensor of Confined Xe

2.3.1 One Xe Atom as a Probe of Anisotropic Spaces in the Solid State

Clathrate hydrates of Xe are crystalline and have distinct cages formed by water molecules. Depending on the conditions, various types of hydrates have been prepared: Structure I, Structure II, H, bromine hydrate. There are altogether 12 distinct cage types in these particular hydrates and Xe in each one has a characteristic average shielding tensor which has the characteristic number of distinct components determined by the nuclear site symmetry at the center of the cage,⁷⁵ based on the analysis by Buckingham and Malm.⁷⁶ Ripmeester *et al.* provided these earliest experimental examples of Xe chemical shift anisotropy for a single Xe atom in cages.^{77,78}

2.3.1.1 Predictions from Pairwise Additivity Model

The shielding tensor of Xe calculated for Xe–Rg pairs and larger collections of rare gas atoms at various Xe–Rg distances, such as Xe₃,¹⁰ Xe in the center of 6 and 8 Ne atoms,¹⁰ and Xe in a helix of 7, 8 and 15 Ne atoms,⁷⁹ provide the basis for the idea that shielding tensor components as well as the isotropic shielding can be duplicated by sums of pairwise shielding tensors over a wide range of distances, although deviations from additivity become significant at very short distances. The first time the concept of additivity of intermolecular shielding was used was for Ar shielding in Ar₃,⁹ but the formal presentation of the “additive dimer tensor model” was made in ref. 80. Other calculations also support the additivity of the isotropic Xe intermolecular shielding in Xe_{*n*} clusters.¹³

The shielding tensor of a single Xe atom located at a specific position (x_j , y_j , z_j), within a cage, helix, or channel constituted of Ne atoms is approximated by a sum of Xe–Ne contributions. In the additive dimer tensor model, the intermolecular Xe shielding is considered to arise from contributions from each atom of the channel by considering each Xe-atom contribution at a time. In other words, it is assumed that the Xe shielding of the j th Xe atom at position (x_j , y_j , z_j), can be calculated by using a summation over the contributions of Xe–Ne dimers, using the *ab initio* XeNe dimer shielding function (for example, the function $\sigma_{\perp}$ and $\sigma_{\parallel}$ from ref. 8) in each case. For example, the contribution to the Xe shielding due to i th Ne atom located at (x_i , y_i , z_i) is given by the *ab initio* tensor component, the function ($\sigma_{\perp}$, $\sigma_{\parallel}$, $\sigma_{\parallel}$)_{XeNe} (evaluated at r_{XeNe}). The derived expressions turn out to be very simple geometric factors coupled with $\sigma_{\perp}$ (evaluated at r_{XeNe}) and $\sigma_{\parallel}$ (evaluated at r_{XeNe}). For example,

$$\sigma_{XX} = \left[\frac{(x_i - x_j)^2}{r_{ij}} \right] \sigma_{\parallel} + \left\{ \left[\frac{(y_i - y_j)^2}{r_{ij}} \right] + \left[\frac{(z_i - z_j)^2}{r_{ij}} \right] \right\} \sigma_{\perp} \quad (2.5)$$

$$\frac{1}{2} [\sigma_{XY} + \sigma_{YX}] = \left[\frac{x_i - x_j}{r_{ij}} \right] \left[\frac{y_i - y_j}{r_{ij}} \right] (\sigma_{\parallel} - \sigma_{\perp}) \quad (2.6)$$

Terms like these are summed to include all the atoms in the channel. The $\sigma_{\perp}$ and $\sigma_{\parallel}$ are functions of distance. We have used a sum of inverse even powers of r to fit the *ab initio* values of Xe–Rg shielding components but some other functional forms, such as sums of exponentials, may be used as well. Then the Xe shielding response in an external magnetic field (B_0) along a particular chosen direction (θ , ϕ) with respect to the crystal frame can be calculated as follows:^{81,82}

$$\begin{aligned} \sigma_{B_0}(\theta, \varphi) = & \sigma_{XX} \sin^2 \theta \cos^2 \varphi + \sigma_{YY} \sin^2 \theta \sin^2 \varphi + \sigma_{ZZ} \cos^2 \theta \\ & + \frac{1}{2} [\sigma_{XY} + \sigma_{YX}] \sin^2 \theta \sin 2\varphi + \frac{1}{2} [\sigma_{XZ} + \sigma_{ZX}] \sin 2\theta \cos \varphi \\ & + \frac{1}{2} [\sigma_{YZ} + \sigma_{ZY}] \sin 2\theta \sin \varphi \end{aligned} \quad (2.7)$$

When the cage enclosing the Xe is a cage of water molecules, as in the clathrate hydrates, the *ab initio* calculations in the best representation of the Xe environment (cage, plus all waters hydrogen bonded to the waters of this cage, plus a self-consistent set of partial charges representing the remainder of the clathrate crystal) are included in the quantum mechanical calculation of Xe shielding in various positions within the cage and yield an over-determined number of data points such as to fit $\sigma_{\perp}$ and $\sigma_{\parallel}$ to functions of Xe–O and Xe–H distances. In this case, the additive dimer tensor formulas mathematically reconstitute the *ab initio* results that have been pre-calculated for various Xe positions within the cage in the clathrate crystallite. The canonical Monte Carlo averaging using the additive dimer tensor model

does not involve additional approximations about the shielding response when used to generate Xe NMR spectra for the same clathrate structures. The generality of the shielding response is assumed when the exact same Xe–O and Xe–H shielding functions and potential functions are used to generate Xe NMR spectra for Xe in *other* structure types of clathrate hydrates.

In another example, additive sums of Xe–C and Xe–H shielding functions used to regenerate the *ab initio* values of the Xe shielding in a large number of configurations for Xe–CH₄ may be used with the best available Xe–CH₄ potential function fitted to Xe–C + Xe–H terms to predict the temperature dependent density coefficient of Xe chemical shift in CH₄ gas. Comparison with experimental values in Xe–CH₄ mixtures over a wide temperature range provides a test for both the shielding surface and the potential functions. Additional approximations are involved when the exact same Xe–C and Xe–H shielding functions and potential functions are used in a GCMC simulation to approximate the shielding response from the atoms of a cage or channel in which CH₃ groups form the inner surface,⁸³ or CH₂CH₂ groups⁸⁴ or when the exact same functions are used to represent in MD simulations the Xe shielding response in solutions of Xe in liquid alkanes.⁴⁹ While keeping in mind the nature of the additional approximations involved, the additive dimer tensor model serves as a very useful means of predicting average Xe NMR chemical shift tensors for Xe in nanocavities and nanochannels in solid materials. For example, the progression of line shape changes with increasing Xe loading such as those observed for Xe in ALPO₄-11 by Ripmeester *et al.*⁸⁵ were reproduced.⁸⁰ These are the first anisotropic line shape calculations which explicitly took into account the dynamic averaging of Xe shielding response within an atomistic representation of the channels in a crystalline material.

The nature of the functions calculated for the $\parallel$ and $\perp$ components of the Xe–Rg shielding and the assumption of pairwise additivity have formed the basis in our work for general predictions of the qualitative behavior of Xe chemical shifts and its anisotropy as a function of temperature and Xe loading in a wide variety of environments, even before carrying out any simulations, in flat disks, in narrow medium and wider bore pipes, and in pipes with elliptical cross sections.¹⁰ The atoms constituting the channel structure represented by a single type of atom, even a rare gas atom, could provide predictions of line shapes as a function of Xe loading and temperature⁸⁰ which reproduce anisotropic line shapes obtained in experiment under various conditions. Quantitative line shape predictions for various clathrate hydrate structures,²¹ channel structures such as ALPO₄-11,⁸⁰ zeolites SSZ-24 and silicalite,⁸⁶ and crystalline dipeptide nanochannels⁸³ could be obtained for the first time by using the additive dimer tensor model in GCMC simulations.

2.3.1.2 Example: A Xe Atom in Clathrate Hydrate Cage

The model used in the *ab initio* calculations of Xe shielding comes from the neutron diffraction data on Structure I Xe clathrate hydrate, and the

hydrogen positions reflecting the remaining proton disorder were determined such as to follow Pauling's ice rules. The quantum mechanical calculations included the Xe atom, the water molecules that constitute the cage and all the water molecules that are required in order to provide the hydrogen bonding partners of every water molecule in the cage (a total of 40 or 48 water molecules) and the remaining water molecules in the crystal fragment are represented by point charges. Monte Carlo simulations used supercells with $n \times n \times n$ unit cells as the propagating unit to create a periodic lattice. ($n = 4$ for Structure I clathrate and $n = 2$ for Structure II was sufficient to produce a statistically valid result). The ^{73}Xe shielding values are fitted to universal pairwise additive Xe–O and Xe–H shielding functions, and the Monte Carlo simulations to generate the Xe NMR line shapes appropriate to the microcrystalline sample of the experiments used these shielding functions. Pairwise additive potentials of the Maitland–Smith form were used. The line shapes calculated for Xe in the 12 types of cages in clathrate hydrate structures I, II, H, and bromine hydrate, using *the same* shielding functions and *the same* potential functions, are in excellent agreement, in terms of the existence of anisotropy, the sign of the anisotropy, and the magnitude of the anisotropy, with the line shapes observed experimentally by Ripmeester and co-workers in Xe type I hydrate, in Xe–propane type II hydrate, in Xe type H hydrate, and in bromine hydrate.^{77,78,87,88} We have assigned the individual average tensor components to specific axes of the cages or the crystal. While the agreement with the experimental values that can be deduced from the Xe spectra is not excellent in every case, we believe the assignments of relative magnitudes of the components to the specific principal directions are reliable. Such assignments cannot be unequivocally determined from the experimental spectra in many cases. We have established that *the* average Xe shielding tensor of a single Xe atom in a cage reflects the symmetry of the cage itself, as canceling contributions of equal magnitude, and opposite signs, are uniformly included in the averaging process through built-in proper statistical sampling. Thus, the Xe NMR line shapes directly provide information about the symmetry of the cage, in the number of unique components, and in the relative magnitudes of the components parallel and perpendicular to the symmetry axis of the cage itself. The basic ideas about Xe intermolecular shielding in confined spaces derived in ref. 10 are in fact sufficient to make the assignments of relative magnitudes and directions of tensor components for each of the 12 types of cages found by canonical Monte Carlo averaging of quantum mechanical shielding hypersurfaces in the clathrate hydrates. It would be wrong to compare magnitudes of shielding anisotropies in cages with different chemical compositions, however.

2.3.2 Xe–Xe Interactions as a Probe of Anisotropic Spaces in the Solid State

Anisotropy of the inner spaces probed by Xe becomes more obvious when Xe NMR is observed as a function of Xe loading in crystalline pores. This arises

from the Xe shielding response from other Xe atoms being quantitatively more deshielding than most atoms constituting the inner surface of a pore. The average Xe shielding anisotropy at full loading becomes very pronounced. For any given architecture of the atoms constituting the pore, at a fixed temperature, the magnitudes of the components of the average shielding tensor change with Xe loading in a *predictable* way under certain conditions.¹⁰ The general predictions from our analysis of the Xe tensor components and line shapes that result from considering the anisotropic Xe shielding response from Xe-wall and Xe-Xe interactions have been applied to observations of Xe in various real systems with channels of symmetrical and also elliptical cross-sections, for example aluminophosphate molecular sieves (AlPO₄-5, -31, -11, and -41) and their corresponding silicoaluminophosphate (SAPO) variants,⁸⁹ rhombus-, and square-shaped cross-section channels formed by metal organic frameworks,^{90–92} channels in organic crystals like tris(*o*-phenylenedioxy)cyclotriphosphazene,^{93–96} channels in crystalline inorganic complexes such as Co(en)₃Cl₃,⁸⁴ large ellipsoidal pores connected by elliptical windows in crystalline Zn hexacyanocobaltate,⁹⁷ monitoring the growth of one type of aluminophosphate crystal structure from another,⁹⁸ channels in various crystalline dipeptides^{99,100} and channels formed by *para*-acylcalix[*n*]arenes assemblies.¹⁰¹

2.3.2.1 Xenon in a 1-Dimensional Narrow Bore Channel

For 1-dimensional channels, we considered the model of an idealized smooth pipe of uniform circular cross-section (which we have designated as a narrow bore relative to the van der Waals diameter of the Xe atom, such that the low energy position for the Xe is along the pipe axis). In such a channel, no two Xe atoms can occupy the same plane perpendicular to the channel axis; that is, the Xe atoms cannot pass each other within the channel. We predicted the number and relative magnitudes of the tensor components as follows. The only electrons which can provide contributions to the Xe shielding response are those electrons in the plane passing through the Xe nucleus and perpendicular to the direction of the B_0 . At zero loading, $\delta_{\parallel} > \delta_{\perp}$ since the ring of atoms in the plane passing through the Xe nucleus and perpendicular to the channel axis are greater in number and closer, giving rise to a greater deshielding (larger chemical shift $\delta_{\parallel}$) while channel atoms in the plane containing the Xe nucleus and passing through the channel axis are fewer and farther away. At full loading we predicted $\delta_{\perp} > \delta_{\parallel}$; with increasing Xe loading at constant temperature, the $\delta_{\parallel}$ remains unchanged, while the $\delta_{\perp}$ progresses smoothly and monotonically from the value at the zero-loading limit to the value at the full loading limit. The Xe shielding response from the electrons of Xe atoms in the channel above and below the Xe nucleus becomes more pronounced with increasing probability of finding Xe in those regions. The Xe shielding tensor component along the direction of the channel axis arises entirely from the electrons of the ring of atoms of the channel in the plane of the Xe nucleus. For a pipe of uniform diameter, this component remains unchanged,

irrespective of how many other Xe atoms are in single file motion in the channel. In at least some cases, the single-file diffusion of Xe atoms have been well characterized by a combination of techniques.^{94,102–104} See also the chapter by Bowers on single file diffusion in this book.

There are several well-known examples, although the molecular crystal channels are by no means smooth: crystalline dipeptides L-Ala–L-Val and its retro analog L-Val–L-Ala, several other binary dipeptides, and the organic molecular crystal tris(*o*-phenylenedioxy)cyclotriphosphazene (TPP). Experimental observations of Xe line shapes as a function of Xe loading in these channels do indeed show the behavior described above for dipeptides Ala–Val and Val–Ala,⁸³ in other binary dipeptides,^{99,100} and in TPP.⁹³ Grand canonical Monte Carlo simulations using quantum mechanical shielding surfaces reproduce the respective behaviors found experimentally as a function of Xe loading for dipeptides L-Ala–L-Val and L-ValLL-Ala,⁸³ other binary dipeptides L-ValLL-iLeu, L-iLeuLL-Val, L-iLeuLL-Ala, L-LeuLL-Ser, L-ValLL-Val, L-AlaLL-iLeu,¹⁰⁵ and in TPP,¹⁰⁶ and also in the channels of the ionic crystal $(\pm)\text{-[Co(en)}_3\text{]Cl}_3$.⁸⁴ Among zeotypes, ALPO₄-31 has channels with nearly circular cross-section in which Xe chemical shift as a function of loading and temperature behaves as predicted.⁸⁹

Deviation from the predictions of the idealized smooth narrow bore pipes can be expected, especially when the channel consists of cells connected by narrowed regions. At low temperatures, the Xe tend to stay in the low potential energy cells and traverse across the barriers of the narrowed regions at higher temperatures. The narrowed regions will be sampled more often at high temperatures leading to a temperature dependence of the chemical shift tensor component along the channel axis $\delta_{\parallel}$, whereas no temperature or loading dependence would have been expected for $\delta_{\parallel}$ in the idealized smooth narrow bore pipe. Of course in the narrowed regions the Xe gets closer to the wall atoms leading to a higher $\delta_{\parallel}$ at higher temperatures. This is indeed observed for Xe in a single crystal of TPP oriented such that the channel axis is along B_0 .⁹⁵ In this case, the narrowed regions also have more pronounced quantum mechanical shielding values, leading to a pronounced temperature dependence of $\delta_{\parallel}$. Unlike sealed samples of known Xe concentration (inside, outside and over-all), where the loading and the temperature of the sample can be decoupled, that is, it is possible to observe the loading dependence under constant temperature conditions, in a continuous flow of Xe (as is typical of hyperpolarized Xe experiments) increased loading necessitates lowering the temperature, thus $\delta_{\perp}$ increases with decreasing temperature because of increasing Xe loading.

2.3.2.2 Xenon in Structured 1-Dimensional Channels

Most molecular channels in which Xe has been observed are not smooth narrow-bore pipes. Depending on the anisotropy of the cross-section, Xe chemical shift tensor at near-zero-loading may have two or three distinct chemical shift tensor components. Any ellipticity in the channel cross-section leads to distinguishable $\delta_{\perp}$ and $\delta_{\perp}'$ averages, as seen in

ALPO₄-11^{80,85} and ALPO₄-41,⁸⁹ with respectively 4.0×6.5 and 4.3×7.0 Å openings. As found also in the rhombus-channels of the metal-organic framework MIL-53⁹⁰ at near-zero loading, the tensor component $\delta_{\perp}$, which is the greater chemical shift, is that along the major axis of the cross-section, with the lesser $\delta_{\perp}'$ being that along the minor axis, just as predicted earlier for elongated cross-sections.¹⁰ Other examples of elliptical medium bore channels in MOFs exhibit the same relative order of tensor components perpendicular to the channel axis.⁹¹

When the channel architecture does not permit two Xe to pass each other, then the individual average tensor components as well as the isotropic Xe chemical shift change *linearly* with increasing Xe loading, as was found experimentally and in simulations in the case of Xe in the elliptical channels of ALPO₄-11.^{80,85} and also experimentally in the rhombus channels of MIL-53.⁹⁰ Shielding tensor calculations for the central Xe in the trimer Xe₃ at various Xe-Xe-Xe angles¹⁰ already suggest that when the channel diameter is large enough to permit the Xe nucleus to have a shielding response from the electrons coming from Xe atoms in the same plane or just below/above, then $\delta_{\parallel}$ could change with loading, increasing only slightly up to not quite half-full and increasing much more pronouncedly between half and full occupancy. Even when the isotropic Xe chemical shift increases perfectly linearly with loading, the individual average tensor components behavior with Xe loading can reveal the pea-pod type structure of the channel, as in the case of Xe in ZSM-12 zeolite.¹⁰⁷ Using the same parameters as used for Xe in ALPO₄-11, GCMC simulations for Xe in a ZSM-12 structure leads to the curved behavior of three distinct components with increasing loading individually very similar to experiment, although more accurate potentials would be needed to get the cross-over points to match experimental line shapes.¹⁰⁸

In our earlier work,¹⁰ some of our predictions for *symmetrical near-circular* wide-bore channels were inaccurate because we had not considered averaging of the two perpendicular components $\delta_{\perp}$ and $\delta_{\perp}'$. We have later shown that GCMC averaging leads to only one distinct perpendicular component in the near-circular wide bore case,⁸⁶ for example in SSZ-24. With the same structure but different chemical composition, ALPO₄-5 exhibits also two distinct Xe tensor components like SSZ-24.⁸⁹ Both components $\delta_{\parallel}$ and $\delta_{\perp}$ change with temperature as predicted, since the Xe no longer stays at the center of the channel but is more spread out. As in the narrow bore case, $\delta_{\perp}$ increases with increasing loading. When the channels are extra large pores as in the gallophosphate cloverite (30 Å diameter)¹⁰⁹ then the Xe may be in fast exchange with the gas phase so that the observed chemical shift does not necessarily reflect the internal environment in the channel.

2.3.2.3 Xenon in 2-Dimensional Spaces

In a set of elegant studies Xe explores 2-dimensional space on the surface of a single crystal in a high-vacuum chamber.^{110–112} These challenging experiments by Jänsch and his group are described more fully in a chapter in

this book. With the normal to the crystal surface along the B_0 , the Xe chemical shift ($\delta_{\parallel}$) comes entirely from Xe–Xe interactions, whereas with the plane of the surface along B_0 , the Xe chemical shift ($\delta_{\perp}$) component comes entirely from Xe interaction with the surface atoms of the crystal, in this case the O atoms of the –CO or the –CH₃ groups of the ethylidyne >CH–CH₃ that are chemically bound to the metal surface. GCMC simulations of Xe on a –CO passivated Ir(111) surface and an ethylidyne covered surface provide rotation patterns and Xe tensors which reproduce the experiments.¹¹³ When the surface is a bare metal surface such as Ir(111), there is the additional Knight shift,¹¹¹ which we will not consider here. Thus, for a Xe monolayer or less, $\delta_{\perp}$ is independent of coverage. On the other hand, ($\delta_{\parallel}$) coming entirely from Xe–Xe interactions increases with increasing coverage.

Hectorite forms silicate layers; the open gallery between layers is intercalated by pillars which are bulky counterions. The gallery is a two-dimensional space punctuated by counterions here and there maintaining the separation between layers at 5–7 Å, depending on the counterion. When Xe can enter this space at very low loading, there are only interactions with the occasional counterions that contribute to the Xe chemical shift component along the normal to the layers ($\delta_{\parallel}$). The $\delta_{\parallel}$ increases with increasing Xe loading as contributions from Xe–Xe interactions set in. On the other hand, the components in the plane of the layers ($\delta_{\perp}$) arise from interactions between Xe and the silicate layer above and below which does not change with Xe loading, provided the pillars which determine the layer separation restrict the movement of the Xe atoms to in-plane. Both tensor components are expected to change with temperature. Two studies using hyperpolarized Xe in hectorite with different cations do indeed find that the $\delta_{\parallel}$ increases markedly with increasing Xe loading.^{114,115} As with other continuous flow hyperpolarized Xe measurements, the temperature and loading effects are conflated with one another; lower temperatures are necessarily accompanied by increased loading. This behavior of Xe chemical shift in 2-dimensional spaces was predicted earlier by considering Xe trapped between idealized parallel plates.¹⁰

2.3.2.4 Xenon in Intersecting Channels

The chemical shift tensors of Xe in one-dimensional channels are relatively easy to understand because the Xe atoms explore only one channel at a time when the crystallites are not too small. However, many interesting systems for which Xe serves as a probe of internal space have intersecting channels. In some cases large cavities interconnected by shared small windows or smaller cavities constitute the 3-dimensional space in which Xe atoms move. In some cases, one type of channel intersects an altogether different type of channel, as in silicalite. When extensive averaging through all accessible channel types and intersection regions occurs throughout the crystallite, is it still possible to observe Xe chemical shift tensor information? The answer is yes, of course, even in a microcrystalline sample, provided the crystallites are

large enough so that Xe predominately reports from inside surfaces. An archetypal example of intersecting channels is silicalite (the all-Si form of zeolite ZSM-5), where one set of channels is straight and the other is sinusoidal. By synthesizing larger crystals we were able to observe the 3 components of the average Xe chemical shift tensor at high loading.¹¹⁶ A millimetre-sized single crystal of silicalite with HP Xe at room temperature rotated in a goniometer in the magnetic field traces out the shielding response as a function of angle as given in eqn (2.7),¹¹⁷ providing the highest quality experimental data for comparison with calculations. The experimental crystal rotation patterns are reproduced by our GCMC simulations,⁸⁶ and simulation provides the three tensor components and their directions at near-zero loading in silicalite.

Some internal spaces are highly symmetrical, for example, the large cavities called supercages in faujasite silicates (synthetic 13Y, for example) are each connected to 4 others and the Linde Type A zeolites with cavities each connected to 6 others, forming 3-dimensional networks. Xe chemical shifts in these crystals would have little anisotropy except for the symmetry breaking effects of different degrees of Al/Si substitution requiring the presence of counterions. In these structures, the Xe line shape therefore exhibits no clear singularities, rather some broadening is sometimes observed due to the minor asymmetry caused by the Al/Si substitution. The observed temperature dependence of the Xe chemical shift in 13Y¹¹⁸ has been reproduced by GCMC simulations.¹¹⁹

2.4 The Chemical Shifts of Xe_n in a Cage Reveal Distributions in Porous Materials

The Xe chemical shift that is observed is an average over all the regions explored by the Xe atoms. The greater the extent of averaging the more limited the accuracy of the interpretation of what is observed. For example, under fast exchange between Xe in the gas phase and the adsorbed Xe, we may not be able to directly determine the Xe chemical shift “inside”. When the Xe is in symmetrical cages, there are no observed tensor components that could be used as a check on the interpretation, and one can associate only an isotropic shift with an overall Xe loading. At any given loading, there are actually fluctuations in the distribution of Xe among the pores or cavities, that is, an overall loading of 5 Xe per cage does not mean that every cage has 5 Xe atoms. In order to find out what fraction of cages have 5, what fraction has 4 or 6 or 1 Xe, it would help to be able to see separately the signal from only those Xe atoms in cages containing 4 (or 6 or 1) xenon. For a given overall loading, how does the distribution of occupancies change with temperature? How are those 4 Xe atoms distributed within a cage and how does that distribution change with increasing temperature? When another gas competes with Xe for adsorption, what is the distribution of the two types of molecules among the cages for a given overall mole fraction? The

chemical shift of Xe inside the pores of zeolite 5A, say, at a given overhead pressure of Xe at room temperature is a result of the answers to the above fundamental questions in adsorption into porous materials, but any interpretations we make from this one measurement are untestable. Fortunately we have model systems in which such details can be observed directly. In A zeolites NaA, KA, and AgA, the framework atoms Al/Si = 1 and the cations required for charge balance are respectively Na⁺, K⁺, and Ag⁺. Six of the cations sit in the windows that are shared by adjacent cages, at positions such as to keep the Xe from freely exchanging between cages. The long residence times permit each Xe_n to be separately observed quantitatively in terms of intensity and chemical shift at various temperatures and overhead Xe pressures, thus providing an incredible amount of detailed information which can be used to test any interpretations. Furthermore, fundamental ideas that are revealed for Xe can be generalized to other adsorbed molecules; only the fine details will differ. This fundamental investigation of distributions in adsorption is made possible by the very large chemical shift range of Xe atom itself in a range of environments, spread out over several hundred ppm. Other molecules, *e.g.*, CH₄, can enter the same size pores as Xe but neither ¹³C nor ¹H intermolecular shifts can fan out the separate signals like Xe can.

2.4.1 Xe_n in Zeolite NaA, KA and AgA

Upon observation of 5 well-resolved Xe peaks in the spectrum of xenon in zeolite NaA, Samant *et al.* assigned the lowest chemical shift to one Xe in an alpha cage, and so on to 5 Xe in a cage.¹²⁰ Later observations by Chmelka *et al.* revealed as many as 7 Xe in a cage.¹²¹ We reported the first observation of 8 Xe per cage, and the equilibrium distribution of occupancies of Xatoms in the cages at 300 and at 360 K for low, medium, and high xenon loading. It was found that the experimental distributions differ from the strictly statistical distributions of hard sphere atoms in mutually exclusive specific lattice sites (hypergeometric distribution), or the statistical distribution of freely moving hard spheres in alpha cages with no specific sites. We also reported the temperature dependence of the chemical shift for each of the Xe_n 'clusters'.¹²² The wealth of detailed experimental information in addition to the adsorption isotherm for Xe in NaA permitted the testing of GCMC simulations for reproducing the experimental distributions as a function of temperature, as well as the temperature dependence of the individual Xe_n chemical shifts. In turn, the ability to reproduce all the details lent confidence to the information available from the simulations, such as one-body distributions of Xe in the cages (how is the Xe distributed within the cage?). Without altering the set of parameters describing the *ab initio*-based shielding functions for Xe and the framework atoms³¹ and the set describing the adsorption-isotherm-based potential functions, all data at various overhead gas densities and sample temperatures could be reproduced, without making assumptions of a distribution model.¹²³ The

same experimental and simulation methods were applied to zeolite KA.¹²⁴ Observations of similar distributions and Xe_n chemical shifts in zeolite AgA¹²⁵ could also be reproduced by using the same simulation methods.¹²⁶ The $\text{Xe}-\text{Na}^+$, K^+ , and Ag^+ shielding functions were taken from *ab initio* calculations. When NaA zeolite has been altered by ion-exchange, *i.e.*, Na^+ ions were replaced successively by Ca^{2+} ions, Xe_n chemical shifts discriminate between those cages which have no Ca^{2+} ion *versus* those that have one Ca^{2+} ion and those that have two Ca^{2+} ions, as revealed when magic angle spinning narrowed the lines so as to completely resolve these fine differences for each of the Xe_n .¹²⁷ Further Ca^{2+} substitution of course leads to all- Ca^{2+} zeolite A (so-called CaA or Linde 5A), where Xe can move freely from cage to cage because the Na^+ ions guarding the windows of the cage have been completely removed and replaced by Ca^{2+} sitting within the cage walls. The single Xe peak that results from the extensive averaging in 5A is typically what one could observe in larger pore zeolites at various overhead Xe densities and temperatures.¹²⁸ The distributions of Xe among the cages of 5A will be very similar to those found experimentally in NaA; the only difference is that they are experimentally observable in NaA, but are hidden in the average shift in 5A.

2.4.2 Xe in Competitive Physical Adsorption in Zeolite NaA

Nearly all applications of porous solids in separations and catalysis involve competitive adsorption and diffusion. Since gases are not ideal, mixture adsorption isotherms are difficult to understand and predict. A fundamental view of competitive adsorption should be able to answer the question: for a given mole fraction of A and B in the overhead gas, what is the probability of having m molecules of type B also present in the same pore where there are n molecules of type A, for any m, n combination? The Xe chemical shifts permit us to answer these types of fundamental questions about competitive adsorption. In an unusually fortunate case, it was indeed possible to see the separate peaks for Xe_nKr_m in zeolite NaA.¹²⁹ The relative intensities provide the distributions of occupancies, and the Xe chemical shifts from individual Xe_nKr_m signals permit detailed tests of the GCMC simulations that reproduce these distributions and chemical shifts.¹³⁰ Here, the Kr atoms are large enough to have long residence times within a cage. However, even when the co-adsorbate (Ar, CH_4 , CO_2 , N_2 or CO) can freely move from cage to cage while the Xe_n stay put, it is still possible to find the same type of distribution information as could be obtained in the case of Xe–Kr adsorption. The chemical shift increment between the Xe_n observed in pure Xe adsorption and the $\text{Xe}_n\text{Ar}_{\langle m \rangle}$ peak observed in the Xe–Ar adsorption provides the value of $\langle m \rangle$ for every Xe_n , where $\langle m \rangle$ is the average instantaneous number of Ar atoms visiting a cage containing n Xe atoms.¹³¹ This can be obtained by a combination of the same type of Xe experiments as in pure Xe adsorption and GCMC simulations to verify the interpretations. Added in are the *ab initio* shielding functions and potential functions for Xe–Ar (or Xe– CH_4 ,

Xe-CO₂, Xe-N₂, or Xe-CO) which are used and verified *via* comparison with Xe chemical shift data in these gas phase mixtures.^{23,132} Thus, the Xe chemical shifts provide as detailed a picture of competitive adsorption as has ever been obtained. Comparison of GCMC results against a highly used model, such as Ideal Adsorption Theory, permits quantitative exploration of the limitations of this model for competitive adsorption, and the conditions under which it works well enough. A binary mixture version of the hypergeometric distribution has been proposed which provides useful insight into cases where the co-adsorbed species are quite similar in size, and the conditions under which its limitations become evident have been explored by comparison with GCMC simulation results.¹³¹

Again, the fundamental molecular level observations about distributions of co-adsorbed molecules among the pores of a solid material made possible by Xe chemical shift measurements can be generally applied to competitive adsorption of other binary mixtures. The relative sizes and shapes of the co-adsorbed species must play a part, but some generally applicable conclusions about the detailed nature of competitive adsorption have been found that could be applied to other systems.¹³³

2.4.3 Xe in Exchange among Multiple Environments

Nearly all applications of Xe in porous solids involve two or more environments for the Xe atom, even when the solid sample is chemically uniform and crystalline. In general, there are at least the following: reservoir I: Xe in the overhead gas, reservoir II: Xe between the crystallites (some Xe may be adsorbed on the outside surface of the zeolite), reservoir III: Xe inside the crystallites that are within an exchangeable layer near the outside, and reservoir IV: Xe deep inside the crystallites (incapable of exchanging with the Xe outside, within the NMR time scale). The relative volumes of these reservoirs depend on morphology and size of crystallites, crystallite packing, overhead Xe gas pressure. In addition to exchanges within each reservoir, mass transport in zeolites include the following exchanges: I ↔ II ↔ III ↔ IV. *Only the Xe chemical shift and line shape in reservoir IV is characteristic of the pore or channel.* Therefore, it is best to work with large crystals. How fast the exchange is between Xe atoms inside the crystallite and Xe atoms outside the crystallite depends on the size of the crystallites, the crystallite packing, the overhead Xe pressure, and the temperature. When there are intercrystalline regions with pores or channels of size comparable to the inside channels or pores, then there are several consequences: The intercrystallite pore-like regions can compete with the channels for Xe population. The Xe chemical shift gives the wrong occupancy number (Xe atoms per cavity); apparent Xe occupancy is greater than that actually present inside because significant numbers of Xe are in reservoir II (between the crystallites). A significant number of Xe in reservoir II means that the exchange I ↔ II gives a I/II weighted “gas peak” chemical shift. The ratio of populations III/IV is not negligibly small; the weighting factor for Xe in reservoir IV do not dominate,

so the “adsorbed peak” is not characteristic of the pores or channels. In this case, the peaks observed in the Xe spectrum are due to exchange averaging and do not provide true chemical shifts; the weighting factors are the numbers of Xe atoms in those reservoirs which are exchanging. At extremely low Xe density, there will still be exchange with the gas, but the number of Xe atoms in the gas is nil; the weighting factor for the gas is nearly zero so the observed Xe chemical shift is that of Xe atom in those pores where it has the lowest potential energy. Lowering the temperature slows down all exchanges, but also leads to greater adsorption which can correspond to multiple Xe occupied pores.

In a mixture of porous materials where each constituent consists of crystals large enough that there are only reservoirs I (outside) and reservoirs IVa, IVb, IVc, ... (inside) the Xe chemical shift will report on each constituent independently, as if the other constituents were not present; that is, the chemical potential of the Xe in I will be equal to the chemical potential of Xe in IVa, and also the Xe in IVb, the Xe in IVc, *etc.* In other words, the Xe chemical shift tensor in IVa will reflect only the $\langle N_{\text{Xe}} \rangle_a$ in the channels in that constituent, for example, and the relative overall area under the peak will reflect the total numbers of Xe in that constituent. GCMC simulations of Xe in each constituent at the same chemical potential as for the gas can be carried out independently to obtain $\langle N_{\text{Xe}} \rangle_a$, $\langle N_{\text{Xe}} \rangle_b$, *etc.* The relative areas depend on the relative amounts of constituents multiplied by these occupancies. Note that the relative areas are not direct measures of the composition of the mixture since the chemical potential of Xe within each type of crystalline pore or channel depends on the atomic structure of the latter. The reaction progress from an amorphous phase to $\text{AlPO}_4\text{-5}$ and its subsequent conversion to $\text{AlPO}_4\text{-18}$ was quantitatively monitored by Xe spectroscopy and GCMC calculations of both Xe chemical shift tensors in just this way.⁹⁸

2.5 Conclusions

The Xe chemical shift and its chemical shift anisotropy have been found to be exquisitely sensitive to the environment in which the Xe atom finds itself. We have seen that encoded in the intrinsic shielding response surface is the electronic structure of the system (a supermolecule or a crystal fragment) as a function of nuclear configuration in the immediate vicinity of the Xe. The dynamic averaging encodes further information about the Xe nuclear environment into the observed chemical shift, such as the architecture of the channel, the diameter of the channel, the aspect ratio of the cross section of the channel, the average size of the cage, the average symmetry of the cage, the number of Xe and other molecules in the cage, the electronic structure of the atoms constituting the cavity walls, the Xe coverage on a single crystal surface, the heterogeneity of the sample, and much more. In the solid, the point group symmetry at the center of the cage in which a single Xe atom is trapped determines the number of non-vanishing tensor components and the number of distinct components of the shielding tensor observed.

The dimensions of the cage determine the magnitudes of these non-vanishing components, their relative magnitudes depending on whether the cage is elongated or squat. Dynamic averaging of the Xe inside a semi-rigid cage does not change the relative order of the components. Similarly, Xe line shape signatures in diamagnetic nanochannels reveal many attributes of the channels. The number of unique components at near-zero loading and at high Xe loading provide information about the aspect ratio of the channel cross section (2 nearly circular, 3 if elliptical). One constant tensor component with changing loading means that the channel diameter does not permit two Xe to pass each other. A linear behavior of each component with Xe loading suggests that an orderly arrangement of Xe atoms in the channel is possible, *i.e.*, Xe can sit in register with low potential energy sites along the walls; Xe is unable to do this when the low energy sites are too close together. A non-linear behavior of tensor components with Xe loading suggests a non-uniform channel cross section. The component parallel to the channel axis does not change with Xe loading or with temperature, if the cross section is of uniform small diameter throughout. On the other hand, some constrictions in the channel can cause a strong temperature dependence of this component. In solid porous materials, the Xe chemical shift can provide information about the distribution of Xe atoms among the pores and also the distribution of other molecules sharing the same pores. As we have seen, there is much that Xe intermolecular chemical shift and shift anisotropy can tell us about materials. This sensitivity of Xe intermolecular shifts to the structure and dynamics of its environment is based on the intrinsic sensitivity of Xe shielding arising from the large $\langle a_0^3/r^3 \rangle$ for Xe atoms in the first place, and secondly, to the very steep deshielding behavior with close approach of another atom. Although the CH₄ molecule has roughly the same size as Xe atom and can explore the same cavities, neither ¹³C nor ¹H possesses these two advantages of Xe atom. Hydrogen can get closer to neighbor atoms, but does not have the large number of electrons in p and d orbitals that can provide a strong intermolecular shielding response at the nucleus.

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CHAPTER 3

Spin Exchange Optical Pumping (SEOP) – Concepts and Practical Considerations

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3.1 Overview

This chapter addresses some of the basic concepts of spin exchange optical pumping (SEOP)^{1–3} and starts with a short review of units that may be helpful for scientists working with hyperpolarised (hp) noble gases. A general definition for spin polarization that goes beyond spin $I = 1/2$ systems is provided. SEOP of ^{129}Xe (spin $I = 1/2$)^{2–5} is presented and compared to SEOP of ^{83}Kr ($I = 9/2$)^{6–9} to illustrate the underlying physics of hp noble gas production. The dependence of the spin polarization, P , and the apparent polarization, P_{app} , on the SEOP pressure, noble gas concentration, laser power, and laser linewidth are presented and experimental examples are provided. A practical gas transfer and compression system that enables almost complete extraction of the hp noble gases from the SEOP cell, even if operating at SEOP pressures below ambient, is described. The hp noble gas production concepts

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

portrayed in this chapter should be of interest for pre-clinical and clinical MRI application in biomedical research. However, many of the presented aspects are also relevant for materials science and engineering-related MRI applications. In particular, SEOP experiments with xenon-methane mixtures illustrate the usage of non-inert buffer gases for SEOP.

3.2 A Few Words about Pressure and Gas Density Units

Although the International System of Units, SI (*Le Système international d'unités*), is more than 50 years old, it is often ignored in the context of gas pressures. For example, medical scientists working in pulmonary research often prefer 'cm H₂O' when addressing lung gas pressure during the breathing cycle. This refers to the pressure produced by a 1 cm high column of water, assuming a gravitational acceleration of $g = 9.81 \text{ m s}^{-2}$. Chemists, on the other hand, have a tendency to use the unit of 'Torr', which is the pressure of 1 mm column of mercury, although mercury based pressure gauges are hardly any longer present in contemporary laboratories. The 'Torr' links to 'atm' with a simple integer number, as $1 \text{ atm} = 760 \text{ Torr}$ but not to 'bar', with $1 \text{ bar} \approx 750.062 \text{ Torr}$. To make things worse, the pressure unit of 'PSI' (pounds per square inch, $1 \text{ bar} \approx 14.504 \text{ PSI}$) is commonly used for technical gas handling. Of course, each community is very proficient with their sets of units, however the hyperpolarized noble gas research brings together a very interdisciplinary group of scientist ranging from fundamental physics to biomedical applications. Furthermore, none of these units is an agreed upon unit within the SI system that suggested the metric based '**Pascal**' ($1 \text{ Pa} = 1 \text{ N m}^{-2}$). Historically, the Pascal is not a popular unit although it is actually very convenient with $100 \text{ kPa} = 1 \text{ bar}$, $100 \text{ Pa} = 1 \text{ mbar}$, and 1 kPa is equivalent to $1 \text{ cm H}_2\text{O}$. Ideally, the Pascal would be widely adopted or, alternatively, at least the 'bar' that is not an SI unit but relates to the metric system and our everyday experience.

Unfortunately, when it comes to gas densities, the SI density unit kg m^{-3} is not very convenient. More useful, and still within the SI system, is the *number density*, $[M]$, that provides the number of atoms (or molecules) of a gas M . Under standard conditions (273.15 K, 101.325 kPa) the number density for an ideal gas M is $[M] = 2.6868 \times 10^{25} \text{ m}^{-3}$. To make this more practical, the '*amagat*' is defined as the density of an ideal gas under standard conditions and therefore 1 amagat is equivalent to $2.6868 \times 10^{25} \text{ m}^{-3}$. Note however, historically the *amagat* is defined as the density of the *real* gas or vapour of a particular substance under standard conditions and this definition leads to slightly different values for the gases typically used in SEOP.

3.3 The Definition and Measurement of Nuclear Spin Polarization P

Spin polarization is often described by the difference in the population N^- of the excited state and the population N^+ of the ground state. This leads to the following equation for nuclear spin polarization P :

$$P = \frac{N^+ - N^-}{N^+ + N^-} \quad (3.1)$$

At infinitely high temperatures, $N^+ = N^-$ and therefore $P = 0$, while at absolute zero temperature, the excited state population $N^- = 0$ and therefore $P = 1$ (or $P = 100\%$). No MR signal can be observed if $P = 0$, while the highest possible signal intensity (under otherwise equal conditions) results at $P = 1$. Unfortunately, due to the small difference between the energy levels associated with the spin state in magnetic resonance, the thermal equilibrium at ambient temperatures leads to only a very small polarization P . Fortunately for us, the associated low signal intensities can be strongly improved through hyperpolarizing the noble gas nuclear spin system.

There is, however, a problem with the semiclassical description of the polarization through the spin population difference, as in eqn (3.1). It works for spin $I = 1/2$ systems and, in modified form, for $I = 1$ isotopes but this description breaks down for spin systems with $I \geq 3/2$. A nuclear spin $I = 3/2$ isotope (^{21}Ne and ^{131}Xe) has four energy levels associated with the nuclear spin states and there is a quantum mechanical difference in the probability for the transition between the energy levels. The full quantum mechanical description requires the definition of the spin polarization *via* the magnetization M_z of the nuclear spin ensemble:¹⁰

$$P = M_z / M_z^{T \rightarrow 0K} \quad (3.2)$$

where $M_z^{T \rightarrow 0K}$ is the (maximum possible) magnetization reached at temperature $T = 0$ K. The polarization P defined through eqn (3.2) converges towards zero as the temperature rises to infinite values because there is no net magnetization (*i.e.* $M_z = 0$) for equal population of all energy levels. Eqn (3.2) converges towards $P = 1$ as the temperature approaches 0 K ($M_z = M_z^{T \rightarrow 0K}$). The full form of eqn (3.2) can be found in ref. 11, but for the following discussion Figure 3.1b and c present the resulting polarization curves as a function of temperature for all stable noble gas isotopes at 9.4 T magnetic field strength. Apart from the temperature and magnetic field strength, the polarization also depends on the value of the nuclear spin I and its gyromagnetic ratio γ . Generally, high values for P require low temperatures far below 1 K. Most NMR and MRI applications are not feasible at such low temperatures but hyperpolarization enables high polarization values at high temperatures, independent of the magnetic field strength. A hyperpolarized nuclear spin system is characterized by a very low spin

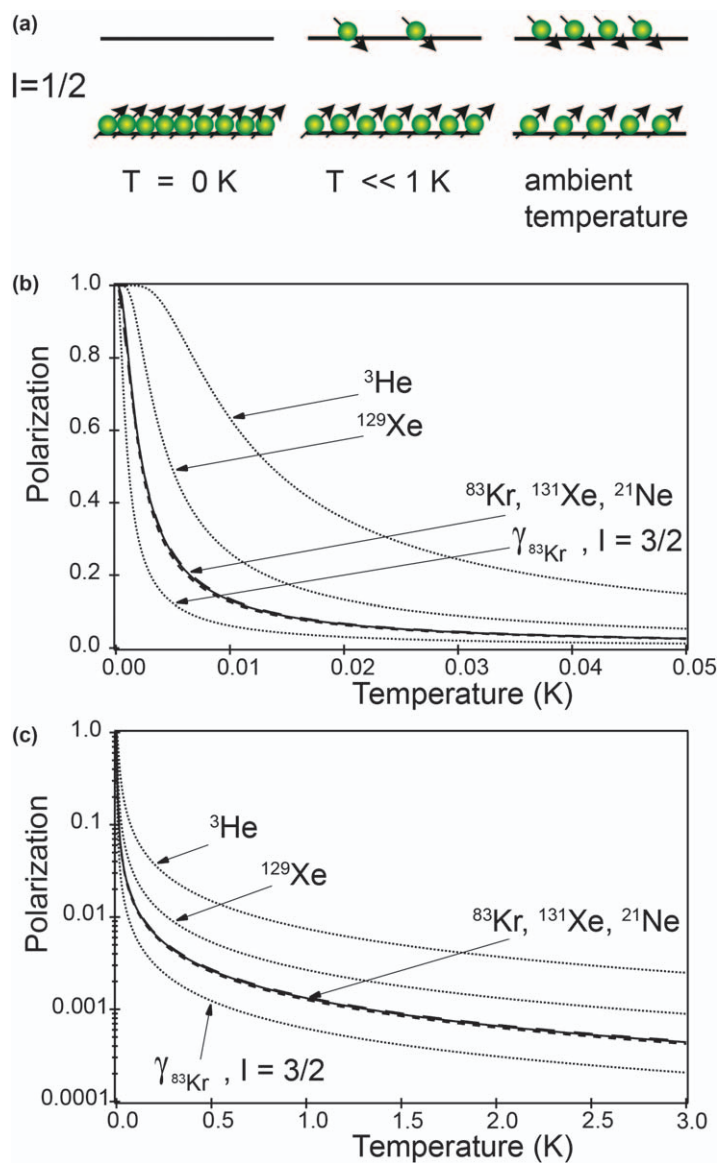


Figure 3.1 The temperature dependence of the spin polarization P at thermal equilibrium. (a) Sketch of the thermal equilibrium population of the energy levels as a function of temperature for a spin $I=1/2$ system. (b) Calculated P values for all stable noble gas isotopes and a 'hypothetical' isotope with the same gyromagnetic ratio as ^{83}Kr but spin $I=3/2$ instead of $I=9/2$ as in the real ^{83}Kr isotope. (c) Same as (b) but for a larger temperature range and a logarithmic scale for the polarization values P .

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temperature that is not in a thermal equilibrium with its environment (usually at ambient temperature). The low spin temperatures of Figure 3.1 can be generated in substances that remained at very low temperature for sufficiently long periods of time to reach the thermal equilibrium. Rapid heating of the system to higher temperature may result in a thermal non-equilibrium state, that we call ‘hyperpolarized spin state’, provided the longitudinal (T_1) relaxation rate of the nuclear spins is slower than the time required for the sample heating. Although this temperature cycling process, known as ‘brute-force’ hyperpolarization, has been demonstrated for xenon,¹² noble gases are typically hyperpolarized either through laser pumping, or as shown recently, through dynamic nuclear polarization^{13,14} (see also the Chapter 24).

In this chapter we will focus on Spin Exchange Optical Pumping (SEOP), but all techniques have in common that they create a very low spin temperature that will exist only temporarily within in a high temperature environment, with typical durations ranging from seconds to many hours. As will be shown at the end of this chapter, this meta-stable, non-equilibrium state with spin temperatures $T \ll 1$ K may exist even in the high temperature zone of a combustion process.¹⁵

Eqn (3.2) describes spin polarization as a function of spin temperature, however this equation in its full form is rather tedious. Fortunately, at ambient temperature where the high temperature condition, $T \gg |\gamma| \hbar B_0 / k_B$, is fulfilled, eqn (3.2) can be reduced to a simpler expression¹¹ for the thermal equilibrium polarization P_0 :

$$P_0 = \frac{|\gamma| \hbar B_0}{3 k_B T} (I + 1) \quad (3.3)$$

where k_B is the Boltzmann constant and $\hbar = h/2\pi$ is the reduced Planck constant. Eqn (3.3), that further simplifies to $P_0 = |\gamma| \hbar B_0 / 2 k_B T$ for a spin $I = 1/2$ system, enables straightforward calculation of the thermal polarization as long as the high temperature condition is fulfilled. However, how is the spin temperature of a hyperpolarized system determined experimentally?

There are a number of innovative methods that, under certain conditions, enable insights into spin polarization even during SEOP at low magnetic field strengths, such as the method devised by Goodson and co-workers.¹⁶ The standard method described in this chapter serves to illustrate the physics but also provides simple means on how to check for the polarization when needed, or to calibrate other methods. This procedure can be followed by any scientist working at magnetic field strengths that are sufficiently high to permit for the detection of thermally polarized noble gases (typically $B_0 > 0.5$ T).

The determination of P of the hyperpolarized gas requires three principle steps:

- (1) The first step is to calculate the equilibrium nuclear spin polarization P at the magnetic field strength and temperature that will be used for an MR measurement of a standard sample containing the thermally

polarized noble gas isotope of interest. For convenience, the thermal equilibrium polarization $P_0^{9.4\text{ T}, 300\text{ K}}$ values for all MR active noble gas isotopes at 9.4 T and 300 K are listed in Table 3.1. The nuclear spin polarization in eqn (3.3) has a linear dependence with magnetic field strength, for example P_0 at 4.7 T is only one half of that found at 9.4 T under otherwise identical conditions. A simple conversion equation for $P_0^{B_0, T}$ at arbitrary temperature T and magnetic field B_0 values (within the range of the validity of eqn (3.3)) is also provided in Table 3.1.

- (2) With the knowledge of P at thermal equilibrium, one now measures the corresponding thermal equilibrium MR signal intensity (*i.e.* the integrated signal intensity that is linewidth independent).
- (3) Finally, the (integrated) signal intensity of the hyperpolarized gas is measured. The comparison between the thermal equilibrium signal and hyperpolarized signal produces the enhancement factor f_{hp} (taking into account any differences in volume, mixture and gas density). The polarization P of the hyperpolarized sample is simply the thermal equilibrium polarization P_0 (eqn (3.3)) multiplied by the enhancement factor, *i.e.* $P = f_{\text{hp}} P_0$. For example, $f_{\text{hp}} = 1133$ measured for hyperpolarized xenon at 9.4 T and 300 K results in $P = 0.01$, *i.e.* 1% spin polarization for the hyperpolarized gas. (Note that in some literature the enhancement factor is defined differently with $P = (f_{\text{hp}} + 1)$, however the difference is of little consequence at $P \gg 1$).

Table 3.1 Parameters for all NMR active, stable noble gas isotopes. The noble gas resonance frequencies are for the pure element approximated to zero gas pressure (note that some texts use XeOF_4 for frequency reference, resulting in higher resonance frequencies for this element). The thermal equilibrium spin polarization $P_0^{9.4\text{ T}, 300\text{ K}}$ for 9.4 T magnetic field strength and 300 K is provided. $P_0^{9.4\text{ T}, 300\text{ K}}$ values are based on the resonance frequencies $\nu_0^{9.4\text{ T}}$ of the pure gas; note that $P_0 = 10^{-6}$ refers to $10^{-4}\%$ spin polarization). For convenience, the equation in the lower right of this table allows for conversion of $P_0^{9.4\text{ T}, 300\text{ K}}$ to the thermal equilibrium spin polarization $P_0^{B_0, T}$ at other magnetic field strengths $B_0(\text{T})$ (or corresponding resonance frequencies $\nu_0^{B_0}$ (MHz)) and temperatures $T(\text{K})$.

Isotope	Nuclear spin I	Natural abundance	NMR resonance frequency $\nu_0^{9.4\text{ T}}$ at $B_0 = 9.4\text{ T}$ of pure gas at zero density	Thermal-equilibrium polarization $P_0^{9.4\text{ T}, 300\text{ K}}$ at 9.4 T and 300 K for pure gas at zero density
^3He	1/2	N/A	304.7 MHz	2.44×10^{-5}
^{21}Ne	3/2	0.27%	31.58 MHz	4.21×10^{-6}
^{83}Kr	9/2	11.49%	15.41 MHz	4.52×10^{-6}
^{129}Xe	1/2	26.44%	110.4 MHz	8.83×10^{-6}
^{131}Xe	3/2	21.18%	32.73 MHz	4.36×10^{-6}
$P_0^{B_0, T} = P_0^{9.4\text{ T}, 300\text{ K}} \frac{\nu_0^{B_0}}{\nu_0^{9.4\text{ T}}} \frac{300\text{ K}}{T} \approx P_0^{9.4\text{ T}, 300\text{ K}} \frac{B_0}{9.4\text{ T}} \frac{300\text{ K}}{T}$				

There are of course practicalities that need to be considered. Thermal NMR signals from noble gas samples are weak and one is advised to create a ‘reference sample’ for this purpose. How this sample should be made usually depends on the noble gas isotope of interest. The most commonly used isotope, ^{129}Xe , relaxes very slowly and hence requires the addition of molecular oxygen as a relaxation agent. The best solution is to fill a thick-wall glass container with ambient pressure of O_2 (approximately 100 kPa or 1 bar above vacuum). The gas phase relaxivity of O_2 for ^{129}Xe is known^{17,18} and 100 kPa (1 bar) of O_2 partial pressure in an O_2 -Xe mixture leads to a ^{129}Xe T_1 time of approximately 3 s, largely independent of $[\text{Xe}]$. Next, xenon gas is added to the container to a total gas pressure of typically a few hundred kPa. For safety reasons it is important to stay well within the pressure limits of the container. Less $[\text{Xe}]$, and therefore a lower total pressure, is needed for a good thermal NMR signal intensity if isotopically enriched gas is used. Noble gas isotopes with a nuclear electric quadrupole moment typically do not require the usage of O_2 as a relaxation agent due to the generally faster T_1 relaxation. Ref. 9 describes examples of ^{129}Xe and ^{83}Kr reference samples, and an example of a ^{131}Xe reference sample can be found in ref. 11. It is good practice to have a reference sample made that is contained in a permanently sealed glass container. This ensures later usage free of concerns about potential gas leakage over time. The NMR recording of the reference sample typically requires signal averaging, and a recycle delay of at least 5 times T_1 is used in order to obtain a meaningful measurement. Ideally, the hyperpolarized gas NMR signal is then recorded in a container of identical dimensions to eliminate any effects from possible detection coil (B_1 field) inhomogeneity. If this is not possible, at least the volume ratio of the thermal sample *versus* hp sample needs to be known. Differences in gas pressure, noble gas concentration, isotopic enrichment, and number of scans N_s used (not $\sqrt{N_s}$ unless one compares signal to noise ratios) between the two samples all need to be factored in.

3.4 Optimizing Spin Exchange Optical Pumping

Generally, one distinguishes between batch mode SEOP and continuous flow SEOP techniques. This chapter will highlight some of the parameters that affect batch mode SEOP, although the general concepts are also valid for continuous flow SEOP. The knowledge of the underlying physics may help users to adjust the technique with particular applications in mind. Specifically, the influence of noble gas concentration, total SEOP pressure, noble gas partial pressure, laser power and laser linewidth will be examined.

3.4.1 SEOP Pressure and Noble Gas Mole Fraction

Figure 3.2 shows the hp spin polarization P as a function of SEOP pressure for various mixtures of xenon (Figure 3.2a) or krypton (Figure 3.2b) with nitrogen. Specifically, Figure 3.2 shows the (near) steady state polarization

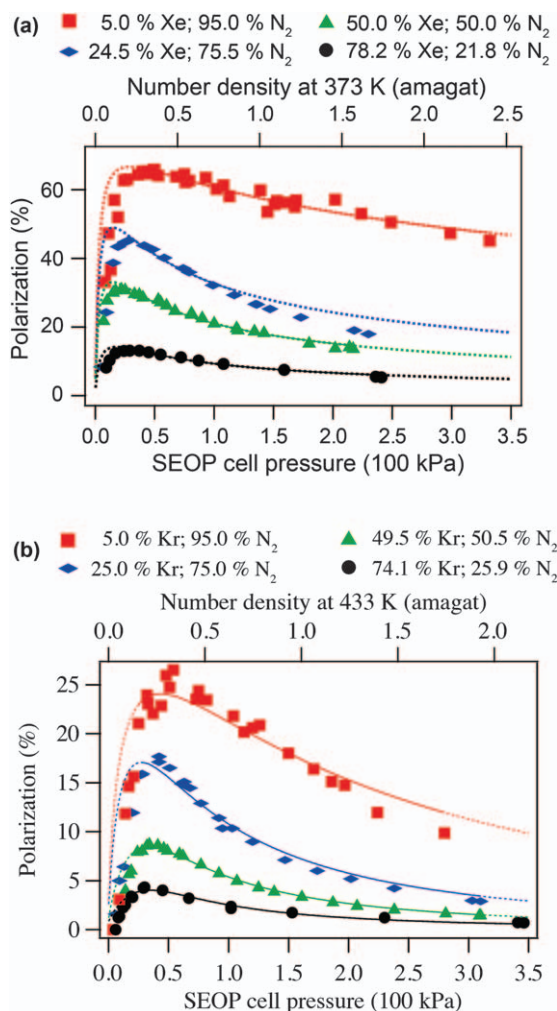


Figure 3.2 The polarization P obtained for various gas mixtures of xenon or krypton with nitrogen as a function of SEOP pressure using 23 W of (incident) laser power. (a) For ^{129}Xe SEOP at 373 K and (b) for ^{83}Kr SEOP at 433 K. The pressure unit used is 100 kPa (*i.e.* 1 bar) and the noble gas density (upper axis) is in amagat defined as the ideal gas density at standard conditions (see text for details).

Images are adapted from work by Six and coworkers in PLoS ONE.⁹

that is obtained after SEOP has taken place for a sufficient amount of time. The time dependence for shorter SEOP times is discussed in the context of eqn (3.8), further below.

Generally, the lower the noble gas mole fraction $n_{\text{Xe}}/n_{\text{tot}}$ in the mixture, the higher its P . This can be understood from the physical phenomena that take place during SEOP. In optical pumping, angular momentum from photons created by circularly polarized laser light is transferred to the electron spin of

alkali metal atoms, typically rubidium (Rb). The polarization of this alkali metal P_{AM} is therefore dependent upon the optical pumping rate γ_{op} that is a function of the laser light absorbed by the gas phase alkali metal atoms. The steady state value of the alkali metal (electron spin) polarization P_{AM} is:^{5,19}

$$P_{AM} = \frac{\gamma_{op}}{\gamma_{op} + \gamma_{trap} + \sum_i \kappa_{sd}^i [M_i]}, \quad (3.4)$$

All terms in eqn (3.4), except for γ_{op} , are destructive and reduce the electron spin polarization. The depolarization rate γ_{trap} caused by radiation trapping is discussed in the following section. For simplicity, a further destructive term, γ_{vdW} , *i.e.* the depolarization rate due to van der Waals complexes of alkali metal atoms with other gas phase atoms is omitted from eqn (3.4).⁹ Most important for an understanding of the general trends in Figure 3.2, are the binary collision of the electron spin polarized alkali metal atoms with other gas phase atoms M_i . These collisions lead to depolarization that is dependent on the specific spin destruction rate κ_{sd}^i times the number density $[M_i]$ of the corresponding atoms. For example, Rb collisions with Kr atoms are about two orders of magnitude more destructive than collisions between Rb and N_2 . Detailed values for spin destruction rates κ_{sd}^i for Rb are summarized in ref. 9, but the relative sizes of atoms usually follow the order:

$$\kappa_{sd}^{Xe} > \kappa_{sd}^{Kr} \gg \kappa_{sd}^{N_2} > \kappa_{sd}^{He} \quad (3.5)$$

As consequence, if the number density $[Xe]$ or $[Kr]$ is high, the polarization P_{AM} will be low unless very high laser power causes γ_{op} to counteract the destructive terms. The nuclear spin polarization P of the respective noble gas isotopes is a function of the alkali metal spin polarization:^{5,19}

$$P(t_p) = \frac{\gamma_{SE}}{\gamma_{SE} + \Gamma} \cdot P_{AM} \left(1 - e^{-(\gamma_{SE} + \Gamma)t_p} \right) \quad (3.6)$$

where Γ is the self relaxation rate (*i.e.* T_1^{-1}) of the noble gas isotope. The spin exchange rate γ_{SE} describes the exchange between noble gas nuclear spins with the electron spins of the alkali metal (see also eqn (3.8)). For sufficiently long periods of SEOP time t_p , the exponential term vanishes and causes eqn (3.6) to become time independent. At this point the steady-state value for P is reached, shown in Figure 3.2 for the respective noble gas isotopes (*i.e.* ^{129}Xe and ^{83}Kr). Furthermore, $P = P_{AM}$ if the spin exchange rate γ_{SE} is much higher than the noble gas self-relaxation rate Γ . For ^{129}Xe SEOP, γ_{SE} is adversely affected by a high xenon densities $[Xe]$, however, Γ is usually very small (see Chapter 7 by Saam for a detailed discussion of Γ for ^{129}Xe). This is different for ^{83}Kr SEOP where $\Gamma > \gamma_{SE}$ due to fast quadrupolar relaxation as described in Chapter 23. Furthermore, γ_{SE} is little affected by $[Kr]$, as discussed in detail in Section 3.4.4.

Higher (steady state) polarization values P for lower xenon or krypton concentrations, as observed in Figure 3.2, are mainly caused by the noble gas density $[NG]$ dependence of the electron spin polarization term P_{AM} in

eqn (3.4). A reduced gas pressure during SEOP also decreases [Xe] or [Kr] and the obtained steady-state polarization P will increase unless the pressures drops below a certain threshold. Depending on the gas mixture used, the optimum pressure for a particular noble gas- N_2 mixture (*i.e.* the maximum of a curve) was found to be between 54 kPa and 22 kPa, below which radiation trapping becomes significant (in addition to accelerated depolarization from van der Waals complexes).⁹

3.4.2 Radiation Trapping

Molecular nitrogen, N_2 , is required to quench the emission of photons from excited alkali metal atoms during SEOP. Photon emission of Rb is discussed in more detail in the chapter by Goodson (see also ref. 20). The triple bonded N_2 molecule is able to adsorb the energy from excited Rb atoms through transfer into its vibrational energy levels. This process prevents radiation trapping that can be destructive to the Rb electron spin polarization. The required $[N_2]$ for radiation quenching is higher for ^{83}Kr SEOP at a temperature of 433 K, where the rubidium density [Rb] in the gas phase is very high, compared to that in ^{129}Xe SEOP at 373 K.⁹ Depending on the SEOP temperature and the N_2 mole fraction in the mixture, at pressures below 60 kPa (0.6 Bar) the nitrogen density $[N_2]$ drops below values that are sufficient for an effective radiation quenching. As a consequence, the obtained polarization values decline strongly at further reduced SEOP pressures. Note that for mixtures with helium as a buffer gas, 20–30 kPa (0.2–0.3 bar; partial pressure) of N_2 is added to prevent radiation trapping. At high SEOP pressures, this condition is fulfilled with 5–10% N_2 in the gas mixture; however, at lower SEOP pressures the lower N_2 mole fraction leads to insufficient $[N_2]$.

3.4.3 Laser Power and Laser Linewidth

The effects of laser power^{21–23} and laser linewidth^{24–27} upon the steady state polarization P are shown in Figure 3.3 for the same ^{129}Xe SEOP conditions as in Figure 3.2a. The laser linewidth and power strongly affect the optical pumping rate

$$\gamma_{\text{OP}} = \int \Phi(\lambda) \cdot \sigma(\lambda) d\lambda \quad (3.7)$$

that limits the steady state polarization in eqn (3.4) and therefore also in eqn (3.6). The laser flux $\Phi(\lambda)$ is a function of both laser power and its spectral linewidth, neglecting the position dependence (due to adsorption within the SEOP cell) for this discussion. The absorption cross-section $\sigma(\lambda)$ is dependent on the alkali metal used, but also on the SEOP temperature and SEOP pressure. Generally, SEOP with diode array lasers strongly benefits from laser line narrowing^{24–27} as these devices exhibit typical linewidths of 2 nm. If the laser linewidth exceeds the D_1 adsorption line width, γ_{OP} in

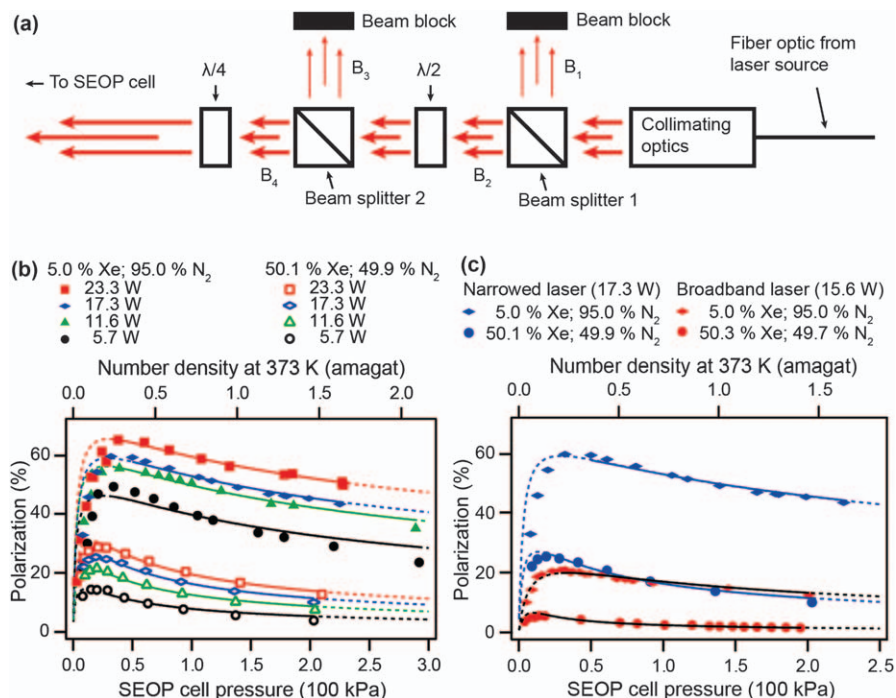


Figure 3.3 The effect of laser linewidth and laser power on the obtained ^{129}Xe nuclear spin polarization P . (a) Schematic of a setup enabling laser power adjustment without affecting other laser emission parameters such as line shape and wave length. The half-wave plate together with beam splitter 2 allows for a controlled reduction of laser power. (b) Experimental data of P for various laser power values using the setup described in (a) and experimental conditions as in Figure 3.2a. (c) P vs. SEOP pressure at two different laser linewidths. A 2 nm wide non-narrowed diode array laser and a 0.2 nm linewidth narrowed laser with similar power were used.

Adapted from work by Six *et al.* in PLoS ONE.⁹

eqn (3.7) will be reduced. A $[\text{Xe}]^{1/3}$, $[\text{Kr}]^{1/3}$, and $[\text{N}_2]^{1/3}$ dependence of the D_1 adsorption line width was found at the SEOP conditions reported in ref. 9 and even ^{83}Kr SEOP at 160 K, benefits from narrowed lasers. Figure 3.3a shows a simple experimental setup that enables studying of the effect of total laser power upon P while keeping the laser linewidth and wavelength constant.

The efficiency of ^{129}Xe SEOP as a function of laser power for two different Xe-N₂ mixtures is displayed in Figure 3.3b. Much higher laser powers (up to 300 W) have recently become available and the use of these higher power lasers will be particularly beneficial for SEOP using mixtures with high Xe concentration. Similarly, the dramatic effect of laser linewidth is demonstrated in Figure 3.3c, comparing a line-narrowed diode array laser with a standard diode array laser. Like higher laser power, narrowed

laser linewidths are particularly beneficial for highly concentrated Xe mixtures.

3.4.4 Time Dependence of the Nuclear Spin Polarization $P(t)$

Thus far, the steady-state polarization $P = P(t \rightarrow \infty)$ was discussed. For short SEOP times, the time dependence of eqn (3.6) will become apparent. This time dependence can be studied in polarization build up curves, where at $t = 0$ no polarization is present in the SEOP cell, *i.e.* $P = 0$. This zero point can be obtained, for example, through radio frequency pulses that destroy magnetization of the nuclear spin ensemble. Figure 3.4 shows an alternative method that may allow for an easier determination of $P(t)$ through ‘inversion-recovery SEOP’. In the inversion-recovery SEOP,⁹ the steady state value of approximately $P/P(t \rightarrow \infty) = 1$ is obtained and the magnetic field for the SEOP process is then inverted at $t = 0$, effectively creating $P/P(t \rightarrow \infty) = -1$.

Fitting of the resulting $P(t)$ provides $(\gamma_{\text{SE}} + \Gamma)$ where the spin exchange rate can be expressed theoretically as follows:²⁸

$$\gamma_{\text{SE}} = [\text{Rb}] \left(\frac{\gamma_{\text{RbNG}}}{[\text{NG}]} \left(\frac{1}{1 + br} \right) + \langle \sigma v \rangle \right) \quad (3.8)$$

There are two types of events that can cause spin exchange between the alkali metal electron spin and the nuclear spin of the noble gas atom. Simple binary collisions lead to spin exchange that is expressed through the binary exchange rate $\langle \sigma v \rangle$. The contribution of $\langle \sigma v \rangle$ to the overall spin exchange rate γ_{SE} is not affected by the noble gas number density [NG]. The second contribution to γ_{SE} comes from the existence of relatively long-lived Rb-NG van der Waals complexes during which spin exchange can also take place. The associated exchange rate constant, γ_{RbNG} , is much larger than $\langle \sigma v \rangle$ but its contribution is diminished at a high noble gas density [NG] because collisions with the noble gas atoms will break up the van der Waals complexes and will therefore shorten their life time. Collision with N_2 molecules will also contribute to this ‘break up’ and the corresponding term is included in eqn (3.8) through the ‘characteristic pressure’ b and the ratio $r = [\text{N}_2]/[\text{NG}]$. A review of literature values can be found in ref. 9 but here it suffices to say that xenon atoms are more potent in reducing the van der Waals complex contribution than molecular nitrogen. Therefore, diluting Xe with N_2 will increase γ_{SE} . The situation is reversed for the Kr- N_2 system. However at the conditions studied in this chapter, the spin exchange rate γ_{SE} for ^{83}Kr SEOP is completely dominated by the binary collision exchange rate.⁹ As a consequence, the inversion recovery curves shown in Figure 3.4b are little affected by SEOP pressure and gas mixture. This is different for ^{129}Xe SEOP where high [Xe] (*i.e.* high Xe mole fraction, high SEOP pressure, or both) reduces γ_{SE} and therefore slows down the build up (or inversion recovery) process. Low [Xe] is therefore advantageous for reducing the SEOP time required to reach the steady state polarization. Furthermore, the rate constants

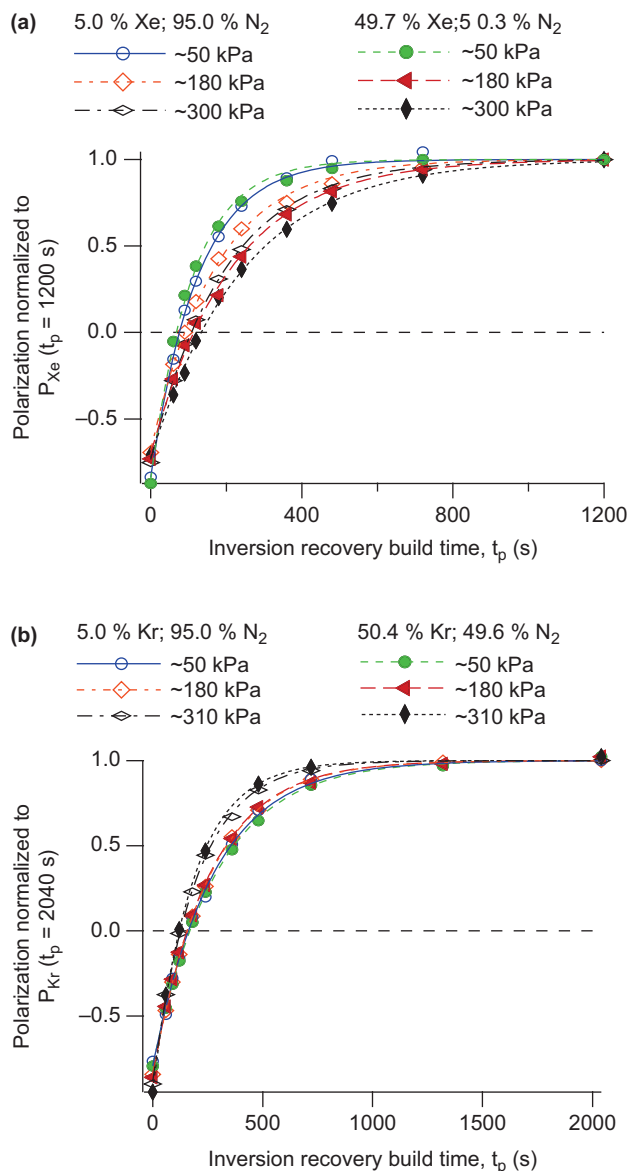


Figure 3.4 The time dependence of the nuclear spin polarization, P , using inversion recovery SEOP for (a) ^{129}Xe and (b) ^{83}Kr at conditions described for Figure 3.2.

Taken from Six *et al.* from PLoS ONE.⁹

$\langle\sigma v\rangle$ and γ_{RbNG} are 2–3 orders of magnitude smaller for ^{83}Kr SEOP compared to those for ^{129}Xe SEOP. This is the main reason behind the high temperature of 433 K required for ^{83}Kr SEOP, since high temperature leads to high $[\text{Rb}]$ values that increase the spin exchange rate γ_{SE} in eqn (3.8).

Furthermore, a speedy SEOP is crucial for the hp ^{83}Kr production due to fast T_1 relaxation of this isotope. Although increased temperatures will also speed up ^{129}Xe SEOP, the high temperatures are detrimental to the Rb spin polarization and will reduce the obtainable steady state polarization. As a consequence, there is an optimal temperature for SEOP that will differ widely between the various noble gas isotopes.

3.5 Cryogenic-free Production of hp Noble Gases

3.5.1 Cryogenic hp Gas Separation

The findings of Figure 3.2 are summarized in the schematic shown in Figure 3.5. A high noble mole fraction will lead to low P (Figure 3.5a), while a dilute gas mixture (Figure 3.5b) allows for high spin polarization. However, due to the high dilution, the hyperpolarized noble gas needs to be separated from the other gas(es) of the SEOP mixture. This is usually accomplished through cryogenic separation at liquid nitrogen temperature (77 K), where xenon freezes but the other SEOP gases (N_2 and in some cases He) are removed through evacuation. Reheating the gas leads to highly polarized, pure xenon gas. This process is well-established^{22,29} (see also Chapter 5) but there can be situations where a cryogenics-free approach may be considered:

- (1) Although the cryogenic separation process is straightforward in a physics laboratory, it adds technical complications to the already complex SEOP procedure taking place in a clinical or pre-clinical

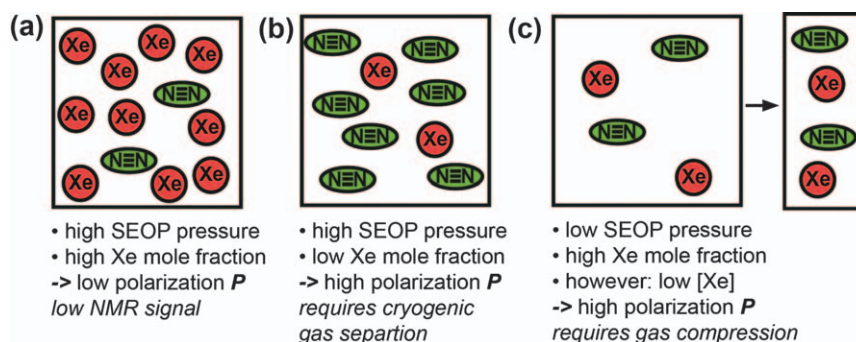


Figure 3.5 A sketch of the expected outcome of various SEOP conditions. (a) A high xenon mole fraction at high or moderate SEOP pressure leads to a high number density $[\text{Xe}]$ and hence to low values for P . (b) A low (dilute) xenon mole fraction at high or moderate SEOP pressure leads to a low number density $[\text{Xe}]$ and hence to high values for P . However, this step requires cryogenic separation to obtain high signal intensities. (c) A high xenon mole fraction at low SEOP pressure leads to a low number density $[\text{Xe}]$ and hence to high values for P . Cryogenic separation is less important for (c) but recompression to ambient pressure is needed for biomedical applications.

environment. This can and has been solved through good engineering, however it typically requires costly equipment.

- (2) Cryogenic separation does cause some losses in polarization. In simple setups, often up to 1/3 of the polarization, P , is lost^{30–32} (see Chapter 7 by Saam for a discussion of ^{129}Xe relaxation in the solid state). As in (1), good engineering is needed to improve the hp gas recovery.
- (3) Using very high laser power, high polarization values can be obtained even at high xenon concentrations. This reduces the need for cryogenic separation.
- (4) Hp ^{83}Kr cannot be separated cryogenically using liquefied nitrogen (77 K), since $T_1 < 10$ s for this quadrupolar isotope at this temperature^{33,34} that is too short for this purpose. Although substantially longer T_1 times are present at lower temperatures, very high losses will be expected upon reheating during transition back to the gas phase. Once again, one could think of good engineering to solve this but it would come with a particularly high price tag.

The results of Figure 3.2 indicate an alternative low cost solution, even at medium laser power (*i.e.* 23 W) used in the reviewed work. Eqn (3.4) requires that the destructive term $\kappa_{\text{sd}}^{\text{NG}}[\text{NG}]$ is kept low to obtain a high P . This can either be achieved at high pressures and low noble gas mole fraction or, alternatively, at high noble gas mole fraction and low pressure, as shown in the schematic in Figure 3.5c. However, low pressure SEOP will require subsequent compression of the gas mixture to at least ambient pressure if it is used for inhalation as a contrast agent in pulmonary MRI, for example.

3.5.2 The Apparent Polarization P_{app}

A 25% Xe–75% N_2 mixture with a ^{129}Xe spin polarization P will result in only 1/4 of the MR signal intensity compared to the signal arising from pure xenon gas with the same polarization P (assuming otherwise identical conditions). This fact can be taken into consideration by defining an ‘apparent polarization’ P_{app} that accounts for the dilution factor of the noble gas:⁹

$$P_{\text{app}} = P \times \frac{[\text{NG}]}{\sum_i [M_i]} \quad (3.9)$$

P_{app} is the spin polarization P multiplied by the noble gas dilution factor or, for that matter, by its mole fraction. If a ^{129}Xe polarization of $P = 44\%$ is obtained in a 25% Xe–75% N_2 mixture, the resulting apparent polarization is $P_{\text{app}} = 11\%$. Like P for pure gases, the apparent polarization, P_{app} , portrays the hp noble gas mixture through a universal parameter. The MR signal intensity from any hp xenon mixture with $P_{\text{app}} = 11\%$ is the same as that from pure xenon with $P = 11\%$ (assuming otherwise identical conditions). Figure 3.6 shows the apparent polarization P_{app} at steady state after SEOP of

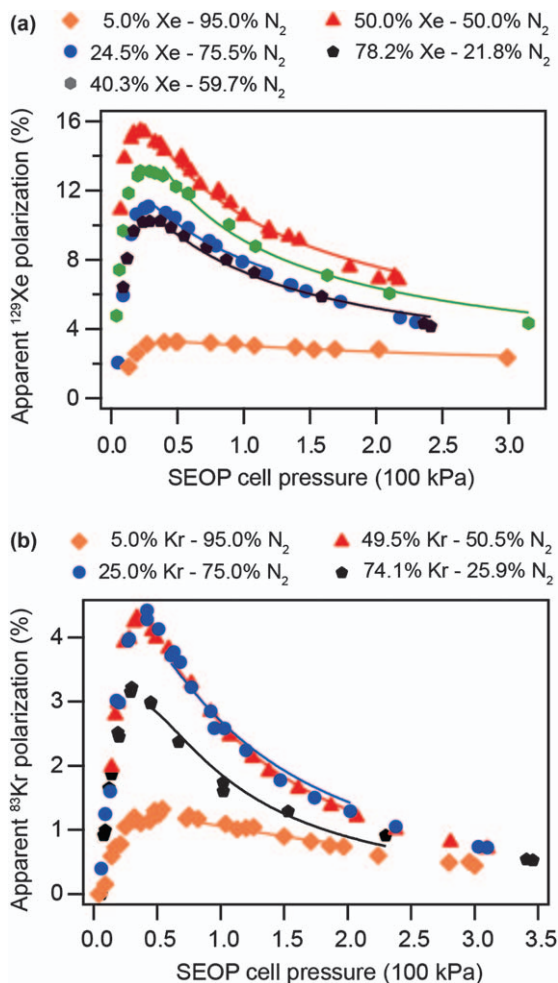


Figure 3.6 The apparent polarization P_{app} as a function of SEOP pressure for various mixtures of xenon (a) and krypton (b) at conditions as in Figure 3.2. The apparent polarization P_{app} is calculated from P multiplied with the dilution factor of the respective noble gas. Taken from Hughes-Riley *et al.*;¹⁸ copyright with the authors.

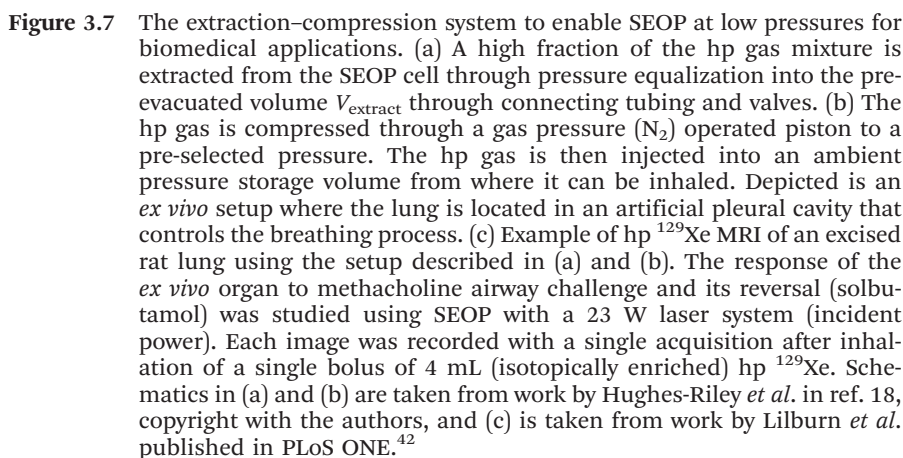
various mixtures of xenon or krypton with nitrogen. At the conditions of Figure 3.6, the highest signal intensity is obtained for ^{129}Xe with SEOP of a 50% Xe–50% N_2 mixture that results in $P_{app} = 15\%$ if a low SEOP pressure of 22 kPa (0.22 Bar) is used. These P_{app} values were generated through SEOP with 23 W incident laser power. Note that higher laser power may shift the most favorable SEOP mixtures towards higher xenon concentration, as discussed in the context of Figure 3.3, and may allow also for higher SEOP pressures as shown by Goodson and co-workers.²³

For ^{83}Kr , as shown in Figure 3.6a, the best results were obtained with either 50% Kr–50% N_2 or 25% Kr–75% N_2 mixtures.⁹ Between the two mixtures, the 1:3 dilution is an obvious economic choice if expensive isotopically enriched ^{83}Kr is used.

For ^{83}Kr SEOP, the batch mode setup is crucial because of low γ_{SE} rates but also because of the short T_1 relaxation times of this isotope when moving through the transfer tubing with high surface to volume ratio. The batch mode setup allows for optimizing (*i.e.* increasing) the ^{83}Kr SEOP times and it permits independent shortening of the transfer times through rapid extraction, as explained in the next section. However, for ^{129}Xe the concepts discussed thus far can also be transferred to continuous flow SEOP, including SEOP at pressures below ambient, as shown in the pioneering work by Fujiwara and co-workers³⁵ (see Chapter 17). However, generally the problem with SEOP below ambient pressure is the need for recompression, as elaborated in the following section.

3.5.3 Extraction and Compression of hp Noble Gases after SEOP

A requirement for low pressure SEOP, as illustrated in Figure 3.5c, is the ability to return the pressure of the gas mixture back to ambient in order to enable biomedical usage of the hp gas. The requirement for hp gas compression is not new, nor is it limited to biomedical applications, and has long been addressed by the community working with ^3He metastability exchange optical pumping (MEOP) that typically takes place at pressures well below ambient.^{36–38} The problem is actually two-fold: not only is it required to reach ambient (or higher) pressure, the hp noble gas mixture also needs to be extracted from the SEOP cell. The latter problem exists even if batch mode SEOP is performed above ambient pressure. For example, if SEOP is performed at 200 kPa (2 bar) and the hp gas is subsequently transferred through simple pressure equalization into an ambient pressure environment (using a Tedlar bag, for example), only 50% of the hp gas (or less if one takes the dead volume of the transfer tubing into account) of the hp gas will actually have been used. The problem of extraction and compression has been solved by Fujiwara and co-workers^{35,39,40} (see Chapter 17) for ^{129}Xe SEOP using a diaphragm pump. Their technique enables continuous flow of below ambient pressure SEOP with subsequent, continuous compression to ambient. However, all previous techniques are not applicable to ^{83}Kr SEOP because of the short T_1 relaxation time of this isotope but Figure 3.7 shows a workable solution. Briefly, a pre-evacuated volume V_{extract} that is significantly larger than the SEOP cell volume, is used to extract the hp gas mixture (Figure 3.7a). A connecting valve between the SEOP cell and V_{extract} is opened, allowing the gas to expand rapidly into V_{extract} through pressure equalization. The Rb vapor is rapidly removed from the gas phase through condensation in the transfer tubing (further studies need to determine whether additional



filters are needed for safe clinical application). After gas extraction, the connecting valve is closed and V_{extract} is reduced through a pneumatic piston, Figure 3.7b. The piston allows for compression to a preselected gas pressure and for subsequent injection of the hp gas into an ambient pressure gas storage container from where it can be inhaled. It should be noted that after gas transfer, V_{extract} may potentially serve as a low pressure hp ^{129}Xe storage device, in line with the low pressure relaxation work by Saam and co-workers⁴¹ (see Chapter 7).

Examples of the usage of the extraction–compression system are shown in Figure 3.7c for hp ^{129}Xe MRI of a methacholine challenged excised rat lung (see also ref. 42). An example of the extraction–compression system applied to hp ^{83}Kr MRI of an excised rat lung can be found in ref. 43 (see also Chapter 23).

3.6 Methane as a Buffer Gas in ^{129}Xe SEOP

Buffer gases used for noble gas SEOP are typically N_2 or He-N_2 mixtures. As discussed above, buffer gases serve to keep $[\text{NG}]$ low, and N_2 is also needed for radiation quenching. One of the requirements is that the buffer gas is inert to the very reactive Rb vapor. This is the case for a variety of hydrocarbon compounds, and Figure 3.8 explores SEOP with methane as a buffer gas.¹⁵

Methane mixtures with hp ^{129}Xe have enabled the first hp ^{129}Xe NMR spectroscopy of a combustion zone.⁴⁴ However, the hp ^{129}Xe was mixed with methane after SEOP and the procedure required a fairly high inert gas content in the methane. Ideally, the hp ^{129}Xe should be only a small fraction of the fuel in order not to disturb the combustion process. A solution is to use a mixture of a small percentage of xenon in methane for SEOP. However, as shown in Figure 3.8a, replacing N_2 completely by CH_4 leads only to low polarization values for ^{129}Xe with $P=14\%$. Although this amounts to a reasonable spin polarization, this value is misleading due to the low xenon concentration and one needs to consider the apparent polarization that is only $P_{\text{app}} < 0.7\%$ obtained in batch mode SEOP. The situation changes, if 10% N_2 is added to the SEOP mixture, resulting in much higher polarization with $P=40\%$ and $P_{\text{app}}=2\%$. The mixture of 5% Xe, 10% N_2 , 85% CH_4 yields almost the same polarization as a mixture of 5% Xe, 10% N_2 , 85% He. It was concluded that radiation trapping reduces the obtained spin polarization in the absence of N_2 and this observation confirms that CH_4 is a poor radiation-quenching agent. Since the concentration of N_2 is only 10%, SEOP below ambient pressure is not beneficial because $[\text{N}_2]$ drops below the value required for an effective radiation quenching. For the actual combustion MRI experiment, a slightly-above-ambient pressure was used to enable continuous flow SEOP and the hp gas was fed directly into the combustor within the MR magnet. Continuous flow SEOP leads to approximately 6–7 times lower polarization values compared to batch mode SEOP with a flow rate dependent polarization of 6–7% (*i.e.* $P_{\text{app}}=0.3\text{--}0.35\%$). This value may appear low but due to the continuous flow a steady state combustion process can be maintained and signal averaging (using 90° flip angle pulses) can be applied for tens of minutes. The resulting MR images are displayed in Figure 3.8c and d. Gas velocimetry measurements in the combustion zone¹⁵ may be of interest for heterogeneous catalytic combustion reaction studies or, more generally, for the study of gas phase dynamics and gas temperature distribution in optically opaque heterogeneous catalytic converters.

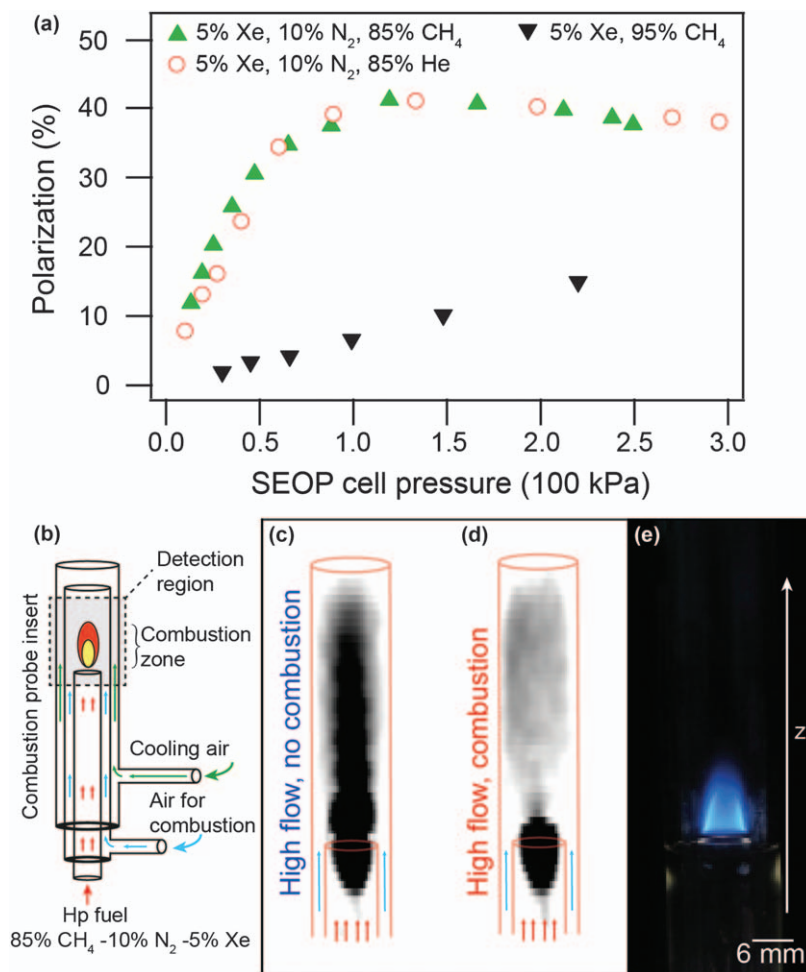


Figure 3.8 Example of hp ^{129}Xe production using a non-inert SEOP gas mixture. This is possible as long as the mixture does not chemically react with the rubidium. (a) A 5% Xe–95% CH_4 mixture leads to low P because methane is a poor radiation quenching agent. However, the mixture containing 10% N_2 results in polarization values that are almost identical to SEOP with the corresponding Xe– N_2 –He mixture. (b) Experimental schematic of a combustion MRI setup shown as an application of ^{129}Xe SEOP with a Xe– N_2 – CH_4 mixture. (c) MRI of the hp Xe flow through the combustor but without a flame present. (d) MRI of the hp Xe flow through the actual combustion zone with a photograph of the flame (to scale) shown in (e). Taken from Stupic *et al.* in ref. 15 with permission from the PCCP Owner Societies.

This last section demonstrates that non-inert gases can be used in the SEOP process as long as the gas mixture does not react with gas phase alkali metal atoms that are not only strong reducing agents but are also able to

start radical reactions. Because of the latter point, the potentially dangerous usage of halogenated gases should not be attempted.

3.7 Conclusion

This concludes the introductory SEOP chapter, with a number of excellent chapters by various experts in this research area to follow. The following chapters provide a good overview of the current state of the art of SEOP and related technology. A completely different route is presented in Chapter 24, where dynamic nuclear polarization (DNP) for hp ^{129}Xe production is explored.^{13,14} Overall, the advances in laser technology, SEOP methodology, and other areas such as DNP, promise to make hp noble gases more readily available and affordable. These are exciting times for scientists who want to engage in the usage of hp noble gases for new areas of research. Therefore, this book is not only focused on SEOP methodology but also on the beautiful research presented by key scientists in hp noble gas NMR spectroscopy and MRI. The covered applications range from material sciences to bio-sensors and to pulmonary MRI.

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CHAPTER 4

Optimization of Pump Cells: Simulation and Experiments

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4.1 Introduction

Hyperpolarized noble gases such as ^{129}Xe can be produced *via* a two-step process denoted as spin-exchange optical pumping (SEOP).^{1–3} Alkali atoms, usually Rb, are optically pumped^{4–6} at the wavelength of their D1 transition which results in an enhanced electron spin polarization (see Figure 4.1, top). These highly spin-polarized Rb atoms are brought in contact with noble gas atoms, *e.g.*, ^{129}Xe . The hyperfine interaction between Rb electron spins and noble gas nuclear spins^{7–11} gives rise to spin exchange processes which finally lead to an enhanced nuclear spin polarization of ^{129}Xe . The quantum mechanical processes underlying the SEOP process have been extensively investigated over the past decades and are understood quite well.^{1–3} However, the efficiency of the SEOP process also critically depends on the aerodynamic and thermodynamic phenomena taking place within the pump cell used in SEOP experiments.^{12,13} A number of authors have, therefore, studied the influence of the various experimental parameters such as pump cell shape and design, laser power, pump cell temperature, gas partial pressures inside the pump cell *etc.* with the final goal to determine the optimum conditions for SEOP experiments. The present chapter

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

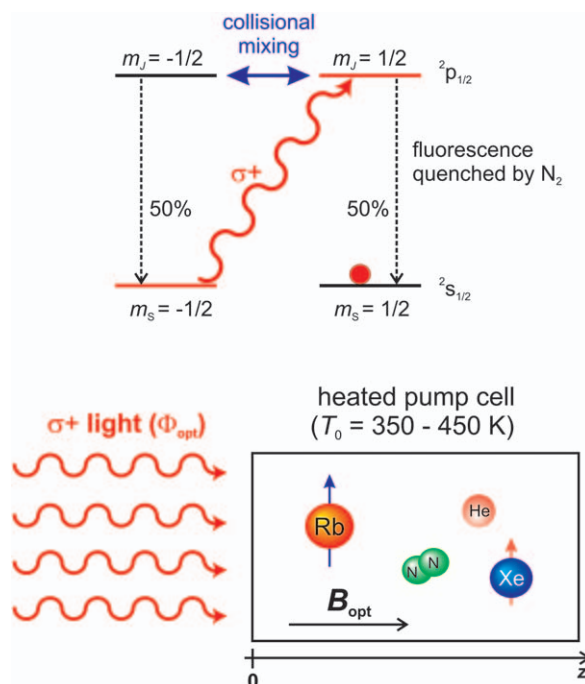


Figure 4.1 Schematic description of the optical pumping process (top) and the major mechanisms resulting in Rb electron spin polarization (bottom).

summarizes the knowledge in optimum pump cell design. The SEOP process includes two basic steps, the optical pumping of Rb and the subsequent spin exchange between the Rb electron spin and the ^{129}Xe nuclear spin. The influence of the experimental parameters upon these two steps will therefore be discussed subsequently.

4.2 The Optical Pumping Process of Rubidium: Where does the Laser Power Go?

The optical pumping of the Rb vapor inside a pump cell requires irradiation of circularly polarized light at an appropriate wavelength, usually, the D1 transition at 794.7 nm. As indicated in the scheme on top of Figure 4.1,^{1,14} this process results in an increased electron spin polarization: since one of the two spin states of the Rb electron spin is continuously emptied by optical pumping ($m_s = -1/2$ if σ^+ -light is used), the other spin state will be enriched after relaxation of the electron spin back into the $5s_{1/2}$ state. In the total absence of any relaxation, the Rb electron spin polarization would finally reach 100%. However, there are a number of processes leading to a continuous “destruction” of the Rb electron spin polarization, as indicated in Figure 4.2. Moreover, the circularly polarized light, which is commonly provided by a laser, will not be absorbed completely by the Rb atoms for

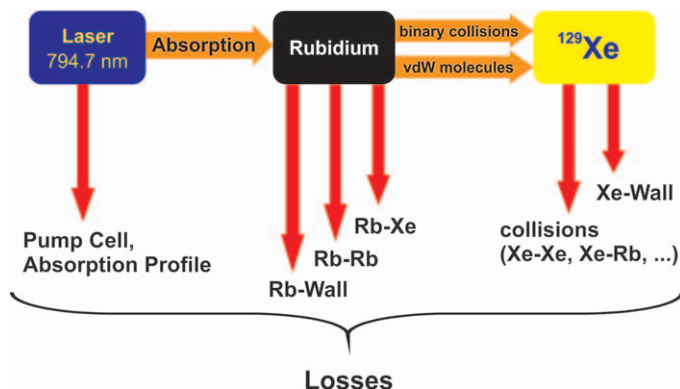


Figure 4.2 Scheme demonstrating the SEOP process and mechanisms resulting in the loss of polarization.

several reasons: On one hand, the emitted laser light spectrum will usually not match perfectly with the absorption spectrum of the Rb. On the other hand, the pump cell will also cause losses by absorption, reflection, and scattering of light depending on the pump cell geometry and used materials. It is, therefore, necessary to optimize the experimental parameters in order to minimize these losses.

As mentioned above, the Rb electron spin polarization obtained in a real pump cell will steadily be diminished by various relaxation processes giving rise to a certain electron spin destruction rate, ρ_{SD} . The equilibrium Rb electron spin polarization obtained in the pump cell therefore depends on (i) the spin destruction rate ρ_{SD} and (ii) the optical pumping rate ρ_{opt} determining the speed of optical pumping.¹⁴

Commonly, it is assumed that the Rb spin completely relaxes if the atoms collide with the pump cell wall. Such collisions result from two processes occurring within a pump cell, namely gas diffusion and convection. Wall relaxation, therefore, depends on the temperature. In order to minimize wall relaxation effects, the surface of the pump cell should be kept as low as possible. Cylindrical pump cells of length l and radius r would exhibit the lowest surface area for $l = 2r$.

Major effects causing electron spin destruction apart from wall relaxation are Rb-Rb, Rb-Xe, Rb-He, and Rb-N₂ collisions.^{8,14-17} The Rb electron spin destruction rate can, therefore, be written as:

$$\rho_{SD} = \sum_i \kappa_i n_i + \rho_{SE} + \rho_{trap} \quad (4.1)$$

The influence of these collisions due to the i -th species can be described by the binary collision coefficient, κ_i , multiplied with the number density n_i of the respective species. Typical values for the binary collision coefficients are reported in the literature,^{8,14-17} for an overview see Fink *et al.*¹⁸ The Rb electron spin polarization is, furthermore, influenced by the Rb-Xe spin exchange ρ_{SE} ¹⁹ giving rise to the desired effect, namely the enhanced Xe

nuclear spin polarization (see Section 4.3). Finally, radiation trapping caused by the unpolarized light emitted by fluorescing Rb atoms gives rise to a corresponding spin destruction rate ρ_{trap} . In order to minimize the influence of radiation trapping, a quenching gas is added – usually N_2 . The influence of N_2 upon the spin destruction rate is described by

$$\rho_{\text{trap}} = \frac{3A}{3 + 7.5 \frac{p_{\text{N}_2}}{\text{kPa}}} \quad (4.2)$$

For the parameter A , values of $33\,000^{20}$ and $40\,000^{18}$ are given in the literature. Usually, N_2 partial pressures of the order of 1–10% related to the total pressure inside the pump cell are applied. This efficiently suppresses the fluorescence. Apart from wall relaxation, Rb–Rb, Rb–Xe, and – at high helium partial pressures – Rb–He collisions are major sources of electron spin destruction.

The optical pumping rate is given¹⁵ by

$$\rho_{\text{opt}} = \int \Phi_{\text{opt}}(\lambda) \sigma_{\text{opt}}(\lambda) d\lambda \quad (4.3)$$

Here, Φ_{opt} denotes the photon flux of the circularly polarized light emitted by the used laser as a function of wavelength and σ_{opt} is the optical cross section of Rb as a function of wavelength. Since the absorption line of the Rb atoms is narrow at low pressures, laser light with a broad spectral profile, as usually provided by laser diode arrays (LDAs), will only partially be absorbed. Typically, LDAs exhibit spectral band widths of 1–2 nm. In such cases, pressure broadening of the Rb D1 transition is advantageous.² Several bar of helium can be applied to the pump cells in order to efficiently pressure-broaden the Rb D1 transition without causing excessive relaxation. The linewidth increase $\Delta\lambda$ caused by helium is approximately given²¹ by the empirical equation

$$\Delta\lambda = 0.038 \frac{\text{nm}}{\text{amagat}} \rho_{\text{He}} f(T) \quad (4.4)$$

where ρ_{He} denotes the helium density in amagat and the temperature function $f(T)$ is 1 at 353 K. 1 amagat is the density of an ideal gas at 101.325 kPa and 273.15 K. That means the helium pressure should be adjusted for optimum laser power absorption depending on the beam profile of the used laser. Several groups have designed pump cells operating at helium pressures of 10–20 atmospheres.^{2,22–24} During the past decades, various experimental approaches were described to substantially narrow the bandwidth of laser diode systems with high output power.^{25–30} For example, the use of a volume holographic grating (VHG) caused the narrowing of an LDA from 2 nm bandwidth (at 32 W output) down to 0.27 nm (26 W).²⁹ Such narrowed LDAs allow production of high volumes of ^{129}Xe by SEOP at low pressures^{29,31,32} taking advantage of the faster Rb–Xe spin exchange at low

pressures (see Section 4.3 below). It should be noted that the best ¹²⁹Xe polarization values on strongly narrowed LDA systems could be observed when the pump light was slightly detuned with respect to the Rb D1 absorption line.^{29,31} This surprising effect was explained by the fact that the “detuning” ensured the best balance between efficient laser absorption *and* global cell illumination to maintain a homogeneously high Rb polarization.²⁹

Taking these considerations into account, the optical pumping process should be optimized such that a Rb electron spin polarization close to 100% can be maintained throughout the entire pump cell. The Rb electron spin polarization (measured in %) at a certain position inside the pump cell after equilibration is given¹⁵ by

$$P_{\text{Rb}} = \left\{ 1 + \frac{\rho_{\text{SD}}}{\rho_{\text{opt}}} \right\}^{-1} 100\% \quad (4.5)$$

That means, the Rb spin polarization depends on the ratio between ρ_{opt} and ρ_{SD} . The optical pumping rate must, for example, be nine times larger than the spin destruction rate in order to maintain 90% Rb electron spin polarization. The Rb and Xe number densities determine ρ_{SD} – apart from wall relaxation. Hence, optimization of the optical pumping process requires to adjust these densities such that ρ_{SD} remains small compared with the optical pumping rate ρ_{opt} , which depends on the available photon flux density of the laser beam. The Rb number density inside the pump cell depends on the vapor pressure of Rb at the given temperature known from the literature.³³

$$\log\left(\frac{p_{\text{Rb}}}{\text{Pa}}\right) = 9.550 - \frac{4132}{T/K} \quad (4.6)$$

Note that the saturation of the gas mixture with Rb is not problematic in static pump cells where the residence time of the gas mixture within the pump cell is long enough for equilibration. However, the maintenance of a defined and constant Rb density throughout the pump cell is a serious problem in continuous flow pump cells (see Section 4.4). The Xe number density will be chosen according to the experimental needs (see Section 4.3).

The laser photon flux density depends on the total laser power and the area illuminated by the laser beam, *i.e.*, its cross section. In many cases, cylindrical pump cells are used which can be fully illuminated by the cylindrical laser beam. During its way through the pump cell, the photon flux of the laser beam will steadily decrease since the Rb electron spin destruction described by ρ_{SD} must be steadily compensated by optical pumping. This results in a decreasing optical pumping rate with increasing penetration depth of the laser beam into the pump cell.¹⁵ This effect limits the optimum length of the pump cell to a certain value depending on the aforementioned parameters determining ρ_{SD} and ρ_{opt} .

4.3 Rb–Xe Spin Exchange

The optically pumped Rb atoms exchange electron spin polarization with the ^{129}Xe nuclear spins due to hyperfine interactions.^{9–11} This takes place during binary collisions and/or *via* the formation of short-lived van der Waals molecules. The latter process is particularly efficient at low pressures. Binary collisions are increasingly important at higher pressures. The nuclear spin polarization of ^{129}Xe after a certain residence time, t_p , in the pump cell is given by the equation

$$P_{\text{Xe}} = \left\{ 1 + \frac{\Delta\rho_1}{\rho_{\text{SE}}} \right\}^{-1} P_{\text{Rb}} (1 - e^{-\{\rho_{\text{SE}} + \Delta\rho_1\}t_p}) \quad (4.7)$$

P_{Xe} depends on the Rb–Xe spin exchange ρ_{SE} rate and the relaxation rate $\Delta\rho_1$ including all the various longitudinal relaxation mechanisms³⁴ contributing to the longitudinal relaxation time T_1 other than the Rb–Xe spin exchange. The spin exchange rate depends on the composition of the gas mixture and on the pressure. It is faster at lower pressures where the Rb–Xe spin exchange process is mainly determined by the formation of van der Waals molecules. The spin exchange rate is furthermore dependent on the Rb concentration in the pump cell. It can be written as

$$\rho_{\text{SE}} = \kappa_{\text{SE}} n_{\text{Rb}} \quad (4.8)$$

The coefficient κ_{SE} is of the order of 10^{-15} – $10^{-16} \text{ cm}^3 \text{ s}^{-1}$, more details are given in the literature.^{2,19} At a temperature of 423 K corresponding to a Rb number density of *ca.* 10^{14} cm^{-3} , spin exchange rates of the order of 0.01 – 0.1 s^{-1} are expected. This corresponds to spin exchange times of the order of 10 – 100 s . The residence time of a xenon atom must obviously exceed $(\rho_{\text{SE}} + \Delta\rho_1)^{-1}$ to obtain a ^{129}Xe spin polarization close to the maximum polarization which would be reached for $t_p \rightarrow \infty$. The ratio between $\Delta\rho_1$ and ρ_{SE} determines this maximum ^{129}Xe nuclear spin polarization. Wall relaxation is a major contribution to $\Delta\rho_1$. In order to reduce this major influence as far as possible, the pump cells are usually coated in order to cover paramagnetic impurities, *e.g.*, with silicone compounds.³⁵ Another contribution is due to the influence of spin rotation interactions Xe–Xe pairs.^{36,37} Another relaxation process occurs if the applied external magnetic field B_{opt} exhibits inhomogeneities, *i.e.*, gradients. Motions of the xenon atoms in these field gradients caused by diffusion and convection processes taking place inside the pump cell give rise to an enhanced longitudinal relaxation.³⁸ Note that spurious amounts of oxygen present in the gas can considerably influence $\Delta\rho_1$.

Taking into account that the described SEOP process depends on a multitude of experimental parameters, it is clear that its optimization deserves special attention. Both fundamental steps – optical pumping of Rb and subsequent spin exchange with the ^{129}Xe nuclear spin as described by eqn (4.5) and (4.7) – are dependent on the position within the pump cell. That means the Rb electron spin polarization as well as the ^{129}Xe nuclear

spin polarization are locally different. Moreover, diffusion and especially convection result in complicated flow phenomena inside the operating pump cell. The description of the local processes which finally result in a certain average ^{129}Xe nuclear spin polarization is therefore a complicated but rewarding theoretical problem. Two fundamentally different cases will be considered, namely (i) static pump cells¹⁸ and (ii) continuous flow pump cells.³⁹ The gas mixture remains in static pump cells during the time t_p until the maximum ^{129}Xe spin polarization is obtained thus resulting in a single batch of highly spin polarized ^{129}Xe . In contrast, continuous flow pump cells are thought to steadily produce a continuous flow of hyperpolarized ^{129}Xe which means that the gas mixture inside a pump cell is steadily replenished.

4.4 Static Pump Cells

For a given pump cell and laser system, the optimization of the SEOP process mainly includes the proper choice of the Rb number density n_{Rb} and of the gas partial pressures inside the pump cell (Xe, N₂, and He). Adjustment of the Rb number density n_{Rb} to the desired value with respect to the optimal optical pumping rate is carried out *via* the temperature inside the pump cell/Rb reservoir (see eqn (4.6)). The Rb density does, however, directly influence the Rb–Xe spin exchange and Rb electron spin destruction rates (see eqn (4.1) and (4.8)). The temperature furthermore influences the collisions between the atoms in the pump cell, giving rise to the various processes discussed above. Moreover, the temperature influences the diffusion and convection processes which are important with respect to wall relaxation. It should be noted that the pump cell is usually surrounded by an oven keeping the pump cell surface at a controlled temperature. However, heating processes caused by laser irradiation in combination with heat transport processes/convection give rise to pronounced temperature gradients between the pump cell surface and interior as well as inside the pump cell which influences the efficiency of SEOP. A computer simulation which takes all these coupled processes into account in a local, three-dimensional manner showed that the mean ^{129}Xe spin polarization throughout the cell increases linearly with the external temperature up to a maximum value depending on the applied laser power. At further increasing temperatures, polarization decays exponentially as can be seen in Figure 4.3. This predicted behavior was found to be in reasonable agreement with experimental results, exhibiting a linear and an exponential regime and a maximum at about the same optimum outside temperature T_0 of *ca.* 420 K. The deviation between the calculated and experimentally determined maximum amounts to 8 K.

Another important parameter is the xenon partial pressure. The more hyperpolarized xenon is produced, the better for many applications. However, the rubidium spin destruction rate also raises with increasing xenon partial pressure. Moreover, the spin exchange rate is higher at low pressures (see Section 4.3). This results in a decreasing ^{129}Xe spin polarization at increasing xenon partial pressure, as has been described by Ruth *et al.*⁴⁰ and Fukutomi *et al.*⁴¹ This effect is demonstrated in Figure 4.4

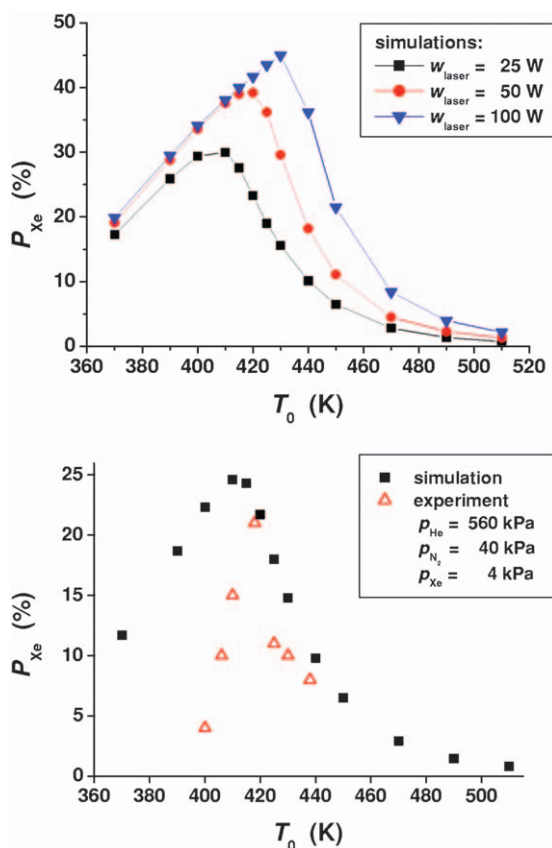


Figure 4.3 Calculated dependence of the mean ^{129}Xe spin polarization on the external temperature for a cylindrical pump cell of 2 cm diameter and 10 cm length. Top: dependence at $p_{\text{Xe}} = 5 \text{ kPa}$, $p_{\text{N}_2} = 13 \text{ kPa}$, and $p_{\text{tot}} = 1 \text{ MPa}$. Bottom: dependence at $p_{\text{Xe}} = 4 \text{ kPa}$, $p_{\text{N}_2} = 40 \text{ kPa}$, and $p_{\text{tot}} = 0.6 \text{ MPa}$, compared with an experiment carried out under identical conditions. Reproduced from ref. 18, with permission from the American Physical Society.

which compares simulated xenon spin polarizations with experimental values determined under identical conditions. Except for the first two values, the data nicely agree. Most likely, the initial deviation from the calculated behavior can be ascribed to the following circumstance: at very low xenon concentrations, xenon atoms are in direct contact with the walls of the cold trap and the sample tube, where the hyperpolarized xenon is frozen out. This may strongly increase the relaxation. Apart from this deviation, our measurements yield the same hyperbolic dependence and very similar values as reported by Fukutomi *et al.*⁴¹ who measured, at 20 W laser power and only 0.1 MPa, the total gas pressure. Our ^{129}Xe polarizations, however, are smaller and decline faster than those of Ruth *et al.*⁴⁰ who have used a five times shorter pump cell of 9.8 mL volume, with 2 W laser power at 100 mbar total pressure. For the experimentalist, however, the crucial parameter is

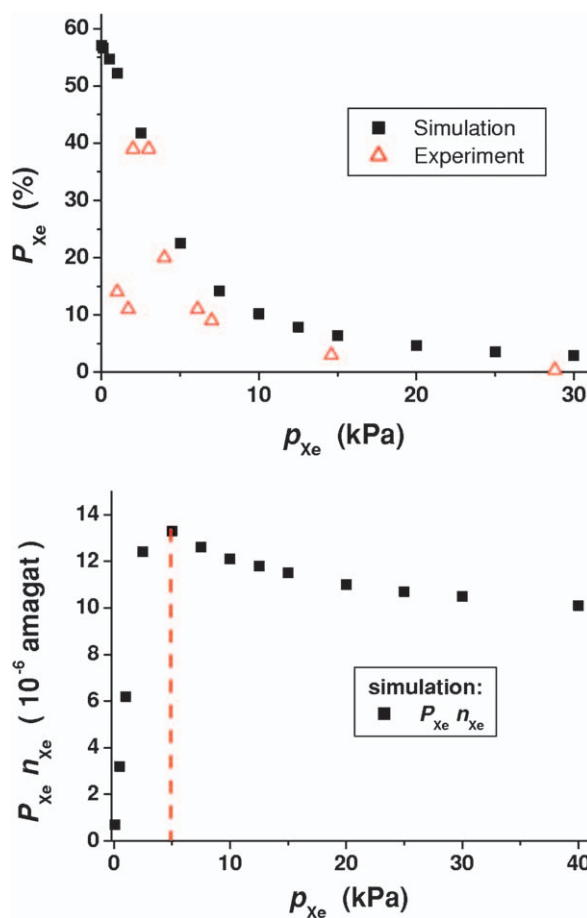


Figure 4.4 Top: dependence of the ^{129}Xe spin polarization on the xenon partial pressure. Squares: simulated data; triangles: experimental data ($T_0 = 420$ K, $P_{\text{laser}} = 25$ W). Bottom: dependence of the product of the ^{129}Xe spin polarization and density in amagat for natural xenon containing 26% of ^{129}Xe on the xenon partial pressure. The vertical line indicates the xenon pressure of about 5 kPa at which the maximal signal intensity is expected. Reproduced from ref. 18, with permission from the American Physical Society.

signal intensity in many cases which is determined by the product of ^{129}Xe density and polarization. The optimum value for the experiment described in Figure 4.4 corresponds to about 5 kPa xenon partial pressure. Recently, Nikolaou *et al.*⁴² described a batch-mode SEOP system which applies a frequency-narrowed LDA system (0.27 nm bandwidth) of up to 200 W laser power. Using this high laser power, the system reaches *ca.* 90%, 50%, and 30% ^{129}Xe spin polarization (inside the pump cell) at 300 Torr, 760 Torr, and 1570 Torr xenon pressure. These are the highest spin polarizations reported yet. It is remarkable that such a high polarization close to one was reached

within this pump cell of *ca.* 500 cm³ volume even at the relatively high xenon pressure of 300 Torr – based on the use of a high-power bandwidth narrowed laser system.

In order to minimize losses of laser power due to radiation trapping, the nitrogen partial pressure must be chosen properly. Laser power absorption at different ratios of helium and nitrogen without xenon were studied.¹⁸ Under the conditions described above (*cf.* Figures 4.3 and 4.4), simulations and experiments gave a minimum absorption at about 10% nitrogen and 90% helium for a constant total gas pressure of 0.5 MPa (*cf.* Figure 4.5). This observation is in agreement with the literature.⁴¹

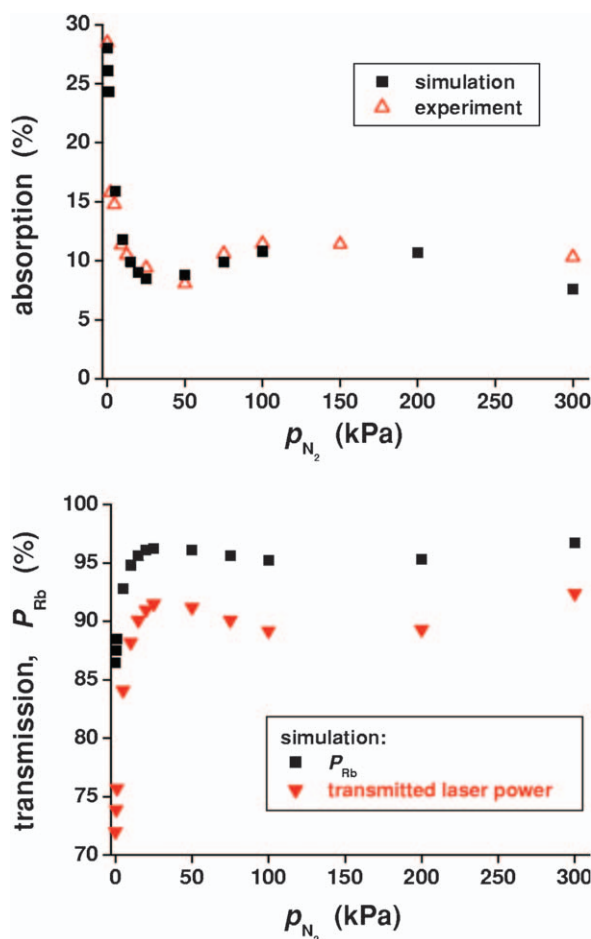


Figure 4.5 Dependence of the laser absorption on the nitrogen partial pressure at a constant total pressure of 0.5 MPa (replenished with helium) in the absence of xenon. Bottom: dependence of the rubidium spin polarization and laser transmission on the nitrogen partial pressure. Reproduced from ref. 18, with permission from the American Physical Society.

4.5 Continuous-Flow Pump Cells

The design and optimization of continuous-flow pump cells requires the consideration of a number of additional problems compared with the static case:

- (i) The volume V of the pump cell divided by the volume flow dV/dt corresponds to the residence time of a xenon atom within the pump cell t_p . This time should exceed the spin exchange time under the given conditions. The influence of the volume flow upon the ^{129}Xe spin polarization was studied by computer simulations on a cylindrical pump cell (see Figure 4.6). It can be seen that there exists a flow rate for each temperature for which the ^{129}Xe spin polarization is maximal. Under the chosen conditions, this optimum flow rate amounts to *ca.* $3 \text{ cm}^3 \text{ s}^{-1}$. For faster flow rates, the residence time of the xenon atoms – especially close to the laser entrance window where the Rb polarization is maximum – is too short. For slower flow rates, the xenon atoms lose too much polarization as the Rb polarization decreases on the way from the laser entrance window to the outlet. The same general trend was calculated and experimentally observed by Schrank *et al.*³²

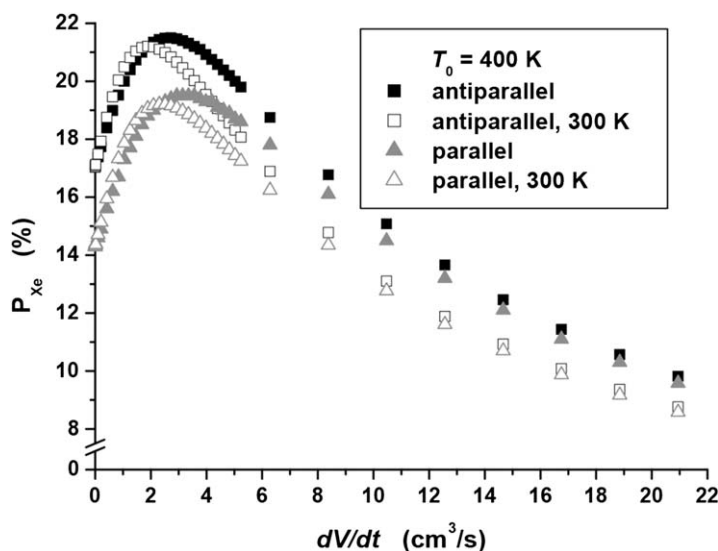


Figure 4.6 Dependence of the ^{129}Xe spin polarization on the flow rate at different flow directions and inflow temperatures. Squares (triangles): gas flow antiparallel (parallel) to the laser beam. Filled (empty) symbols: inflow at oven (room) temperature. Cylinder of the pump cell: 2 cm diameter, 10 cm length, $p_{\text{Xe}} = 5 \text{ kPa}$, $P_{\text{laser}} = 25 \text{ W}$, $T_0 = 400 \text{ K}$. Reproduced from ref. 39, with permission from Springer Verlag.

Note that the simulations also show that a gas flow antiparallel to the laser beam should be more efficient, because the Rb spin polarization increases on the way to the outlet in this case (see Figure 4.6). This principle was applied, for example, in the continuous-flow SEOP devices developed by Ruset *et al.*,⁴³ Imai *et al.*,⁴⁴ Schrank *et al.*,³² Norquay *et al.*,⁴⁵ and Witte *et al.*⁴⁶

- (ii) Another important experimental problem related to the continuous-flow mode is the inhomogeneous Rb distribution in the pump cell. A continuous gas flow results in Rb removal from the pump cell, the maintenance of a constant level of gaseous Rb in the pump cell turns out to be a non-trivial problem. The He/Xe/N₂-gas mixture should hence be presaturated with Rb vapor at the pump cell temperature before entering the pump cell. To illustrate this, one can consider a horizontally arranged, straight glass cylinder of 1 cm diameter which contains a 4 mm-broad streak of liquid Rubidium at its bottom. At a flow speed of 4 cm s⁻¹ corresponding to a flow rate dV/dt of approximately 3 cm³ s⁻¹, efficient saturation of the gas mixture with Rb would require a tube length of about 50 cm.³⁹ Various experimental solutions to this important problem have been presented meanwhile. Ruset *et al.*⁴³ have designed a 6 m-long, spiral-shaped saturator containing numerous Rb puddles. This saturator is wound around the cylindrical pump cell. The saturator is contained together with the pump cell in the same oven which ensures that both are heated to the same temperature. This is advantageous for Rb saturation and with respect to the flow properties in order to avoid turbulences (see (iv) below). Schrank *et al.*³² used a short tubing containing fine quartz glass wool saturated with purified Rb metal. The presaturator is placed inside the oven heating the pump cell.
- (iii) Another experimental problem giving rise to decreasing ¹²⁹Xe spin polarizations can occur at high laser powers.^{47,48} The uptake of energy by the fluorescence-quenching nitrogen gas results in a corresponding production of heat. This local heating can generate dense and highly absorptive Rb clouds close to the laser entrance window. In a chain reaction (“Rb runaway”), these Rb clouds result in further local absorptive heating. Consequently, the pump cell is inhomogeneously illuminated and the ¹²⁹Xe spin polarization drops. It is, therefore, recommendable to remove the Rb from the neighborhood of the laser entrance window, *e.g.*, by local cooling of the pump cell region close to the laser entrance.^{43,46}
- (iv) The temperature of the gas inflow into the pump cell is also important. Low-temperature gas inflow causes density gradients and, hence, turbulences in the pump cell influencing the ¹²⁹Xe spin polarization (see Figure 4.6). Ideally, the gas inflow should therefore exhibit the same temperature as the gas inside the pump cell. This is naturally given if a Rb presaturator (see (ii) above) is used which is kept at the same temperature as the pump cell.^{39,43}

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Large Volume and Continuous Flow Hyperpolarization

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5.1 Introduction

Hyperpolarized noble gases xenon-129 (^{129}Xe) and helium-3 (^3He) have shown great potential to become clinically approved contrast agents for magnetic resonance imaging (MRI) for measuring pulmonary structure and function.^{1,2} Their applicability to MRI was recognized two decades ago,³ and since there has been a challenge to produce highly polarized noble gas in large quantities for sustaining large scale clinical trials in order to demonstrate their capability. Most of the initial research was focused on ^3He because of its higher gyromagnetic ratio and higher attainable polarization through the available methods. However, ^3He supply is very limited, being extracted as a tritium decay product from nuclear weapons programs. A major shortage in 2009 raised awareness within the community about the limited resource and increased the price drastically.⁴

Xenon is a naturally abundant gas, extracted from atmosphere through partial distillation. ^{129}Xe isotope comprises about a quarter of the naturally

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

© The Royal Society of Chemistry 2015

Published by the Royal Society of Chemistry, www.rsc.org

abundant xenon, but its concentration can be further increased through centrifugal mass separation.

Both ^{129}Xe and ^3He gases can be hyperpolarized using a technique called spin-exchange optical pumping (SEOP).⁵ This process requires a circularly polarized laser source emitting at 794.7 nm, which is the wavelength matching D_1 absorption line of rubidium (Rb) atoms. The laser beam propagates along the axis of a magnetic field and illuminates a gaseous mixture containing the xenon gas to be polarized, Rb alkali metal vapor, a gas to quench photo-excited Rb (nitrogen), and optionally a buffer gas (typically helium-4).

The circular polarization of the laser light depopulates Rb ground state levels with opposing spin leaving only one spin orientation which will finally become the polarized state. Concomitantly, atomic interactions between Rb and other atoms (especially xenon) depolarize the Rb, hence the laser must continually replenish the Rb polarized state. When a polarized Rb atom interacts with a ^{129}Xe atom there is a probability that the nuclear spin of the ^{129}Xe atom will acquire the orientation of the Rb electron polarization in a process called spin-exchange. The probability of spin-exchange is significantly increased when the Rb–Xe collision results in a longer-lived van der Waals molecule. This particular process typically dominates the spin-exchange rate in the low pressure operating regime.⁶ Over extended exposure times, the Xe polarization will asymptotically equilibrate toward the polarization of the Rb atoms. Differently from ^3He , the spin-exchange process characteristic for ^{129}Xe is faster by three orders of magnitude, *e.g.*, to achieve saturation for ^{129}Xe polarization can require tens of seconds, while ^3He may require as much as several hours to approach Rb polarization.

The design of the high-throughput clinical xenon polarizer prototype presented here is based on the original counterflow polarizer.^{7,8} There are three distinct functional regions of the polarizing column: a Rb pre-saturator helix, a hot polarizing region, and a gas cooling and Rb condensing region (Figure 5.1) The Rb pre-saturator helix and the polarizing region in the lower

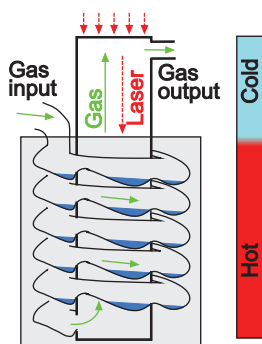


Figure 5.1 Concept of the counterflow polarizer showing the three operational regions: Rb vapor saturating helix (containing Rb puddles), spin-exchange optical pumping heated region, and Rb vapor condensing cold region.

part of the polarizing column are immersed in a silicone oil bath heated to an operating temperature of 140–150 °C. The gas mixture of xenon, nitrogen, and helium enters the system through the glass helix and flows downward through the helix preloaded with puddles of Rb metal. As the gas temperature approaches the oil bath temperature it also saturates with Rb vapor. Upon entering the main polarizing column at its base, it flows upwards towards the polarizing laser light which enters the column through the top window. The spatial distribution of the Rb polarization in the polarizer depends on the local D_1 laser intensity (optical pumping rate) and local spin destruction rate. During optical pumping, the Rb acquires a stable spatial distribution of its polarization along the column with the highest polarization closest to the laser entrance and lower Rb polarization farther away. The xenon atoms from the gas mixture will start building up polarization as they interact with the polarized Rb, achieving their highest polarization at the top of the hot zone. The cold zone is designed to extract the Rb vapor from the gas stream before it exits the laser illuminated area. In the absence of laser pumping, the Rb atoms depolarize within milliseconds and start to further depolarize ^{129}Xe atoms. The counterflow design provides continuous optical pumping of the Rb until it condenses. A powerful laser system would keep Rb polarization at its highest across the whole volume of the cell. However, if the laser is underpowered the polarization of Rb will be distributed with its highest polarization closest to the hot–cold transition region where the laser enters the hot polarization region. Counterflow design is advantageous because the laser entrance coincides with the gas mixture exit, maximizing the accumulated xenon polarization as the gas flows through the system.

5.2 Materials and Methods

Advances in laser technology over the past several decades have enabled commensurate improvements in optical pumping. During the 1980s and early 1990s, optical pumping was performed by increasingly capable technologies: resonance lamps, dye lasers, and then argon-ion pumped titanium-sapphire lasers. By the mid-1990s the optical pumping community transitioned to solid-state diode lasers whose lower cost and higher power efficiency made them well-suited for higher power applications. The large bandwidth of their wavelength output prevented all the light from being utilized. Resonant absorption of optical pumping light depends upon the pressure-broadened linewidth of the absorbing atoms. With absorption linewidths of approximately 0.04 nm for every atmosphere of gas pressure inside the cell, only a small fraction of the light from diode arrays with production linewidths of 2 nm to 4 nm would contribute to optical pumping. In fact, it was preferred to operate in the high pressure regime in order to maximize laser absorption, even though the Rb– ^{129}Xe spin-exchange rate is lower.

Within the last decade, technology for narrowing the output of a diode array bar using wavelength-sensitive elements has been demonstrated. Chann *et al.*⁹ used an afocal telescope to image optical rays onto an angled grating in the Littrow configuration, which then diffracted back to the laser cavity the selected wavelength for amplification. This approach has been used to achieve linewidths as small as 11 GHz (24 pm) for a single diode array bar.

We sought methods to scale up the power output by narrowing a full stack of diode array bars.¹⁰ The transverse dimension of a laser bar stack presented an impediment. An afocal telescope images a spatially extended light source in a plane perpendicular to the optical axis, however the grating is inclined at the Littrow angle. Bars displaced from the optical axis would be out of focus, preventing their light from being perfectly reimaged back on their emitters. The key improvement of our laser system (Figure 5.2) is a step-mirror system within the locking cavity. The main purpose for the step-mirror is to adjust the optical path for each laser bar such that all light rays come into perfect focus on the grating. Another important feature of the step-mirror is that it controls and reduces the amount of the dark space between the emitting diode bars. The step-mirror and feedback grating are mounted together on a motorized rotational stage which provides final adjustment of the overall wavelength for the narrowed laser beam.

A more recent innovation corrects for the “smile” of the diode bars. Manufacturing imperfections in the flatness of the diode bars, so called “smile”, are transformed into angle variations after the fast-axis microlens, and dominate the overall linewidth of the wavelength-locked laser output.⁹ In order to remove this remaining variation, we characterized residual

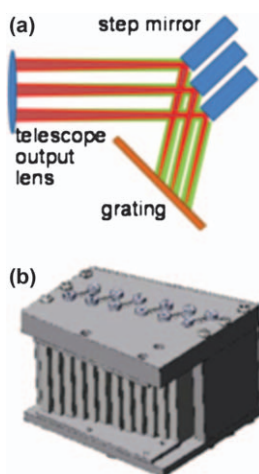


Figure 5.2 (a) Schematic of the step mirror adjusting the optical path lengths (fast axis shown in green, slow axis in red); (b) step mirror assembly corresponding to a 12-bar array.

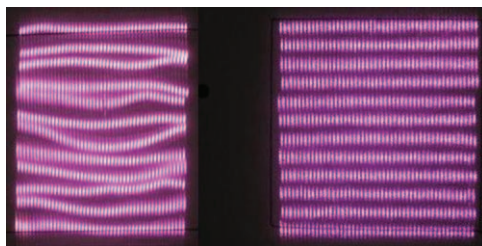


Figure 5.3 Reduction of “smiles” for one 12-bar stack, shown before (left) and after (right) implementing a set of correction plates in front of factory microlenses.

imperfections emitter-by-emitter in the output of each laser bar stack following a prescription by McBride.¹¹ Two parameters were measured: angular deflections caused by laser bar “smile” and greater-than-optimal divergence due to microlens distance variations. A correction plate with a corresponding array of curved prisms was fabricated consisting of unique correction elements for each emitter (PowerPhotonic, Fife, UK). This correction plate was permanently attached 2 mm in front of the laser stack and with excellent results as shown in Figure 5.3.

These innovations are implemented in a system with 24 laser bars each capable of 100 watts free-running output, however in our spectral narrowing system we lose some efficiency and de-rate the power output still further, typically operating around 700 watts. The central wavelength is selected by adjusting the angle of the feedback grating in order to maximize its absorption by the Rb vapor. We observe spectral resolution as narrow as 0.2 nm for individual bars, with an overall width of 0.3 nm.

In order to dissipate the heat from this laser, to stabilize the temperature of the spin-exchange process,¹² and to scale-up the flow, we replaced the single glass column of the first demonstrated unit⁷ with a 14×14 cm² square copper column augmented with internal copper fins (Figure 5.4a). This geometry creates sixteen flow channels with copper walls that transfer very efficiently the heat deposited by the laser into the surrounding oil bath. Additionally, the internal fins (Figure 5.4b) give structural support such that the column can withstand low pressures. This geometry is also a good match for the low divergence laser beam whose shape is given by the stacked CW laser diode arrays. The top and bottom of the column are made as viewport flanges with fused silica windows for laser transparency. Insertion of a glass divider between the top (cold) and the bottom (hot) sections creates a thermal barrier in the column. The one-meter long hot section and the half meter long cold section are precision-machined from oxygen-free copper and brazed together using lead-free Cu-Ag brazing solder for thermal conductivity with the external walls (Figure 5.4c).

We report here a freeze-thaw xenon accumulation subsystem adapted from our previously reported design.⁷ By measuring the volumetric recovery fraction achieved by different glassware geometries, we selected a helical

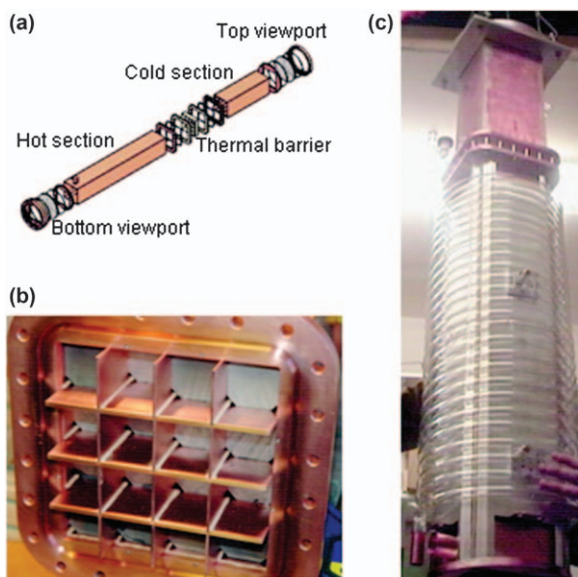


Figure 5.4 Copper polarizing column: (a) overall schematic showing subcomponents; (b) top view of the hot section during assembly. Sixteen individual channels are separated by copper fins. Temporary graphite spacers provide structural support during high temperature brazing. (c) Final assembly includes the glass helix containing the Rb puddles for vapor saturation. The glass helix is connected to the main body of the column at the base.

configuration that offered the highest efficiency for trapping xenon from the lean mixture of flowing gases. Deposition of xenon frost uniformly over the internal surface of the tubes is achieved by slowly raising the liquid nitrogen level over the time of the accumulation process. The cryogenic trap glassware (freeze-out) was scaled-up to an eight-helix ensemble (Figure 5.5b). Over the time of polarized xenon accumulation this is immersed in a liquid nitrogen (LN₂) dewar system which is filled to the top by an automated LN₂ level controlling system. The LN₂ dewar rises slowly over the xenon accumulation time and its motion is driven by a two-axis slide stages with stepper motor and pneumatic piston, and computer controlled *via* a LabVIEW software interface. At the end of the accumulation process the LN₂ dewar is rapidly lowered, moved aside, and replaced by a hot water (60 °C) container which, when in contact with the helix tubes, results in a quick thawing of the xenon back into the gas phase and dispensed into the Tedlar bags. In order to extract as much xenon as possible from the freeze-out system, we have implemented a chasing technique which displaces the xenon remaining in the freeze-out glassware by flowing nitrogen gas. A continuous pressure monitoring system stops the chase if the bags become fully inflated, otherwise the nitrogen flow is timed out and limited to the volume of the glassware.

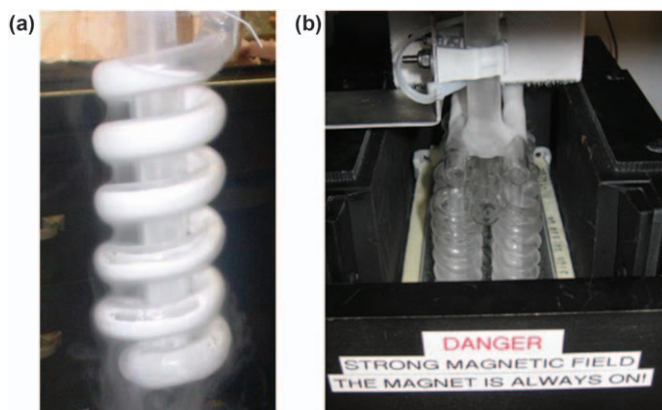


Figure 5.5 (a) Single helical cryogenic trap showing a layer of xenon ice deposited on the inner surface. Part of the xenon ice is already thawed into gas phase uncovering some of the glass walls. (b) The high-flow cryogenic accumulating system is composed of eight parallel helical glass tubes which are gradually immersed in a rising LN₂ dewar, such that the xenon is uniformly distributed along the length of the tubes. A high magnetic field (~ 0.3 T) provided by permanent magnet plates is needed for preserving polarization during phase transition changes.

5.3 Results and Discussion

Copper or metals are not commonly used as “wetted” materials for SEOP systems because of the shortened noble gas surface relaxation times on the order of minutes. We had estimated that the high spin-exchange rates available in the low pressure operating regime would be sufficient to overwhelm the shortened T_1 of xenon on copper. Optimal operating conditions are achieved not only with low overall pressure, but also with low xenon concentrations and high flow velocity.

The prototype high-production polarizer was assembled as a nearly fully automated portable platform (Figure 5.6a) to provide on-site HP ^{129}Xe to clinical research partners. For the imaging experiments, two-litre batches were typically prepared each hour, with polarizing time of 20 minutes. The xenon flow rate through the system was set at 6 litre per hour as standard operating value. Polarizing parameters were: total pressure of 500 Torr, nitrogen flow rate of 2 standard litre per minute (slm), helium flow rate of 4 slm, oil bath temperature 145 °C, laser operating current of 60 amperes corresponding to an output power of approximately 700 watts of narrowed spectrum light. Following the thaw, the HP xenon is dispensed into as many as four Tedlar bags for inhalation. (Figure 5.6b).

Over the last couple of years more than 700 litres of xenon were polarized and delivered to more than 170 human subject participants in the imaging studies. Figure 5.7 shows overall performance of the system as operated at the University of Virginia, where a third-party noble gas polarimeter

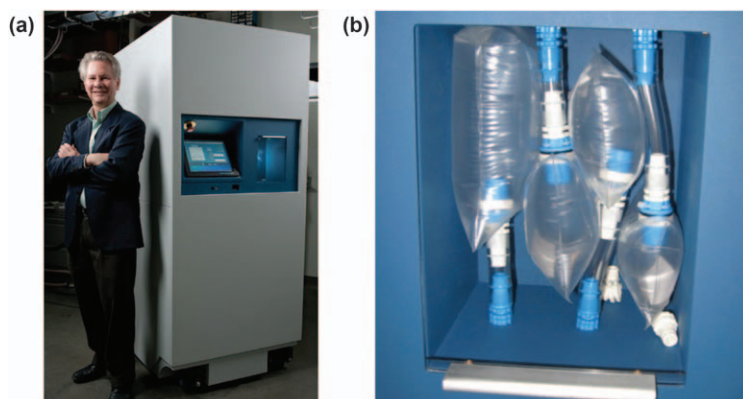


Figure 5.6 (a) Xenon polarizer as a compact portable system presented next to Professor F. W. Hersman, first author of the article and pioneer of the counter-flow polarizing technology. (b) Xenon batch can be dispensed in a combination of four dosing bags. The bags are attached to the connecting ports inside a polarizer niche.

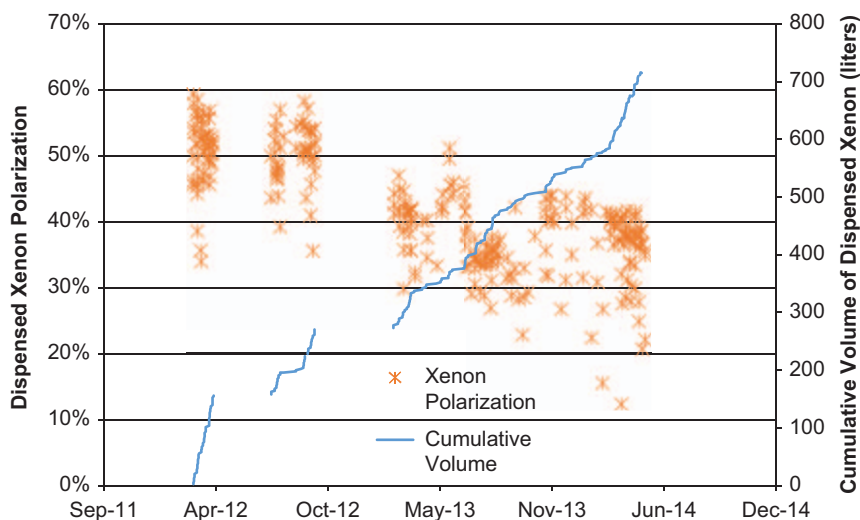


Figure 5.7 Xenon polarizations measured inside the dosing bags with a third-party NMR polarimeter ranged typically from 30% to 60%. While in the first year polarization average to above 50%, in 2013 partial laser bars failure lowered polarizations to 30% to 45%. We acknowledge contribution of Dr Jaime Mata from University of Virginia in supporting polarizer operations and measuring xenon polarization.

(MITI, Durham, NC) was available to measure polarization of xenon directly as dispensed in the dosing bags. Short gap periods in the production timeline are explained by temporary relocation of the system to Washington University in St. Louis for similar studies. Within the last year, performance

of the system decreased unexpectedly. This was recently associated with partial failure of the lasers with only $\sim 75\%$ of the emitters remaining active.

The human imaging studies occurred mainly at the University of Virginia as part of collaborative research to demonstrate safety and efficacy of HP ^{129}Xe in human lung imaging. All the human experiments were conducted under informed consent, following approved IRB protocols and Investigational New Drug protocols approved by the FDA to the University of New Hampshire and Xemed LLC. We imaged healthy subjects and patients with lung diseases including COPD, asthma, cystic fibrosis, and sickle cell disease. The subjects inhaled up to one litre of HP xenon, usually supplemented with oxygen to maintain its concentration at the atmospheric level or/and with nitrogen to achieve a specific lung inflation. Comparisons of ventilation anomalies between HP ^{129}Xe lung ventilation images and comparable images acquired with HP ^3He at two sites revealed that images with xenon were better at conspicuously delineating ventilation defects.^{2,13} The high polarization and production rate from this prototype ^{129}Xe polarizer enabled novel imaging protocols that focused on xenon solubility in tissue and blood, and that are not possible with ^3He .^{14,15}

In conclusion, we report technical developments that have enabled scale-up of production of HP ^{129}Xe achieving polarizations in the 50% range at rates of several litres per hour. A prototype polarizer implementing these developments was first deployed in 2011, and has since been relocated to several HP gas imaging sites performing clinical research. Collaborative studies are ongoing using this polarizer to demonstrate safety and efficacy for a range of lung imaging diagnostic applications.

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Spin-exchange Optical Pumping at High Xenon Densities and Laser Fluxes: Principles and Practice

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6.1 Introduction

Once limited to the realm of fundamental physics experiments, hyperpolarized (HP) noble gases have been exploited for a wide range of applications across NMR and MRI. In most cases, hyperpolarized noble gases are prepared by spin-exchange optical pumping (SEOP). In SEOP the spin populations of noble gas nuclei are driven far from equilibrium *via* the selective absorption of circularly polarised light by an alkali metal vapour and

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

subsequent spin-exchange with the noble gas—thereby endowing the HP gas with enhanced magnetic resonance sensitivity.

Of particular interest is the xenon-129 isotope ($I = 1/2$): ^{129}Xe is especially attractive for NMR/MRI applications because its NMR parameters (chemical shift and relaxation) are highly sensitive to its surroundings. Although all noble gases are essentially chemically inert—enabling them to be used as safe, non-destructive probes of samples and living organisms—xenon is also well-known for its avidity for interacting with the cavities and surfaces of molecules and materials. Indeed, xenon is soluble in lipid membranes, blood, and other tissues, and can even be used as a *solvent* in its liquid or supercritical phases. Moreover unlike ^3He , which suffers from a world-wide shortage, ^{129}Xe is relatively inexpensive and naturally abundant.

Yet the production of HP ^{129}Xe is not without its challenges. First, gas-phase collisions between Xe and the alkali metal atoms that are needed for spin-exchange are far more likely to result in the *loss* of electronic spin polarization of the metal *without* conserving the spin angular momentum for the noble gas—making it increasingly difficult to achieve high polarizations at high Xe densities. And while this problem can be mitigated by the application of ever-higher resonant laser fluxes, the resulting increases in energy deposition within the OP cell can give rise to phenomena that are poorly understood in terms of their impact on SEOP efficiency. Focusing primarily on work from our laboratories over the last decade, this Chapter reviews fundamental, experimental, and technical aspects governing SEOP in the “extreme” regimes of high xenon density and resonant laser flux—particularly in the context of generating HP ^{129}Xe for NMR/MRI applications.

6.2 Background

6.2.1 A Brief History of SEOP for Noble Gas Hyperpolarization

The ability to use light to polarise electron spins was first demonstrated by Kastler,^{1,2} who also considered the possibility of transferring this non-equilibrium spin polarization to nuclei.² This prediction was soon realised in heavy metal vapours^{3,4} and noble gases like helium and xenon.^{5–7} In general, noble-gas OP may be performed *via* two approaches: SEOP and metastability-exchange OP (MEOP);^{6,8} however, MEOP—while useful for hyperpolarizing ^3He (and also demonstrated with ^{21}Ne)⁹—is not expected to be practical for heavier noble gases.

Following Kastler's work,^{1,2} Bouchiat, Carver, and Varnum⁵ discovered that the nuclei of ^3He present in an alkali metal OP cell slowly became polarised, resulting from collisions and spin exchange (SE) with the electronically spin-polarised alkali atoms. Later Grover showed that this approach could be used to generate spin-polarised nuclei in xenon as well, at a much higher rate.⁷ SEOP processes have since been studied further in pioneering work by Happer, Cates, Walker, and many others.^{10–16}

6.2.2 A Primer of Relevant Theoretical SEOP Concepts

SEOP is a two-step process (Figure 6.1): in the first step (Figure 6.1(a and b)), angular momentum is transferred from resonant circularly polarised (CP) light to the electron spins of an alkali metal (AM) vapour. For example, when σ^+ CP light at the AM D_1 transition (Figure 6.1a, nominally at 794.76 for Rb and 894.3 nm for Cs) is applied in the presence of a weak magnetic field, population is selectively driven from $m_j = -1/2$ in the ground state ($S_{1/2}$) into $m_j = +1/2$ in the excited state ($P_{1/2}$, neglecting the AM nuclear sublevels). The magnetic field (B_0) is applied parallel (or anti-parallel) to the direction of light propagation that defines the quantization axis for the light-matter interaction. Collisions between the AM atoms and other gas-phase species effectively equalise the populations of the excited-state m_j sublevels, which in turn equalises the ground-state repopulation rates. Depletion of the ground $m_j = -1/2$ sublevel and concomitant accumulation of population in the ground $m_j = +1/2$ sublevel rapidly reaches steady state, leaving the AM vapour electronically spin-polarised (D_2 OP is described in Figure 6.1b).

The steady-state AM electronic spin polarization [$P_{AM} = (N_+ - N_-)/N_{Total}$, where N_+ , N_- refer to populations of the $m_j = +1/2$, $-1/2$ states], will be a function of position in the cell:¹⁷

$$P_{AM}(z, r) = \frac{\gamma_{OP}(z, r)}{\gamma_{OP}(z, r) + \Gamma_{SD}}, \quad (6.1)$$

where z and r respectively define distances across the cell and radially from the central axis. Here, $\gamma_{OP}(z, r)$ is the OP rate per AM atom at position (z, r) , given by:¹⁸

$$\gamma_{OP}(z, r) = \int \Phi(z, r, \nu) \cdot \sigma_0(\nu) d\nu, \quad (6.2)$$

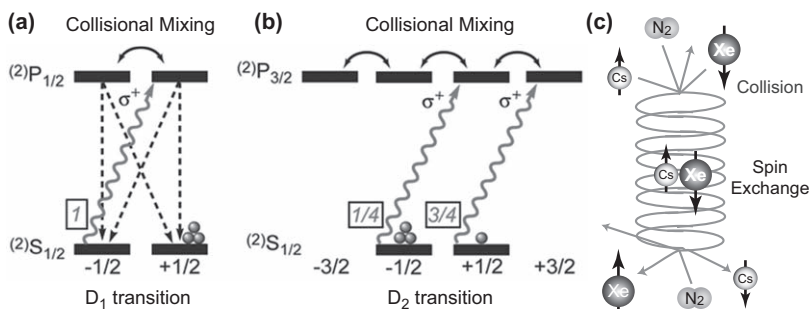


Figure 6.1 Polarization of alkali metal electronic spins *via* D_1 (a) or D_2 (b) excitation with circularly-polarised light. With D_2 OP, population is driven from *both* ground sublevels at a 3 : 1 ratio, so the maximum P_{AM} value is 50% (cf. 100% for D_1), and the sign of the polarization is inverted (from ref. 53). (c) Transfer to Xe nuclei by spin exchange;¹⁰ Cs is depicted as the AM atom, and N_2 is shown as the third body facilitating formation/breakup of vdW complexes.

where $\Phi(z, r, \nu)$ is the laser flux per unit frequency (ν) at position (z, r), and $\sigma_0(\nu)$ is the absorption cross-section; also, Γ_{SD} is the electron spin destruction (SD) rate, which in the bulk is dominated by collisions with other gases (including xenon) in the cell:

$$\Gamma_{\text{SD}} = \sum_i k_{\text{SD}}^i \cdot [M_i], \quad (6.3)$$

where k_{SD}^i is the SD rate per collision with species (i), and $[M_i]$ is its number density. Indeed, collisions with *heavy* species—particularly xenon—will generally dominate the alkali vapour SD rate when present, as $k_{\text{SD}}^{\text{Xe}}$ is nearly 600 and ~ 2600 times that of N_2 and He, respectively.^{19,20}

In the second step of SEOP (Figure 6.1(c)), the presence of a noble gas in the OP cell—hereafter assumed to be ^{129}Xe —will naturally result in gas-phase collisions between Xe and the electronically spin-polarised AM atoms. During such collisions, there is a chance that spin exchange will occur between the polarised electron spin of the AM atom and the unpolarised nuclear spin of the ^{129}Xe atom. This spin exchange is mediated by Fermi-contact hyperfine interactions.¹⁰

The chance of a mutual spin flip during a given AM/Xe encounter is low¹³ ($\sim 5\%$ when binary collisions are dominant); however, because ^{129}Xe T_1 's are typically long (minutes to hours), P_{Xe} can build up over time¹⁸:

$$P_{\text{Xe}} = \langle P_{\text{AM}}(z, r) \rangle \cdot \left(\frac{\gamma_{\text{SE}}}{\gamma_{\text{SE}} + \Gamma_{\text{Xe}}} \right) \cdot \{1 - \exp[-(\gamma_{\text{SE}} + \Gamma_{\text{Xe}})t]\}, \quad (6.4)$$

where the overall relaxation rate constant is partitioned into a sum of γ_{SE} (the Xe-AM SE rate) and Γ_{Xe} (comprising all of the other, deleterious relaxation terms, and here is equivalent to $1/T_1^{\text{Xe}}$). Within an OP cell, the primary contributors to Γ_{Xe} will generally be wall collisions, with diffusion through local field gradients and Xe-Xe (and Xe-other) gas-phase collisions and persistent dimers generally providing much weaker contributions.^{21–23} However, in more recent years the wall-collision pathway has been sufficiently suppressed in some circumstances to allow multi-hour cell T_1 's to be achieved (*e.g.*, Figure 6.7), in which case the persistent dimer pathway can become a limiting factor—see ref. 21–23 as well as the Chapter on Xe relaxation in this work.

The Xe-AM gas-phase collisions may be three-body (*e.g.* Figure 6.1(c)—necessary for the formation of short-lived van der Waals (vdW) complexes) or two-body in nature, depending upon the experimental conditions. The efficiency of AM-Xe polarization transfer is governed by the SE rate:^{12,17,24}

$$\gamma_{\text{SE}} = [\text{AM}] \cdot \left\{ \frac{\gamma_{\text{AMXe}}}{[\text{Xe}]} \left(\frac{1}{1 + br} \right) + \langle \sigma v \rangle \right\}, \quad (6.5)$$

where $[\text{AM}]$ is the AM density (*e.g.* typically $\sim 10^{11}$ – 10^{14} cm^{-3} for Rb),¹³ γ_{AMXe} is the rate contribution from three-body interactions, $\langle \sigma v \rangle$ is the velocity-averaged binary SE cross-section, and for Rb OP cells with Xe/ N_2 gas mixtures, $br = (0.275) \cdot (\text{N}_2 \text{ pressure}) \cdot (\text{Xe pressure})^{-1}$; the last term takes into

account the relative abilities of Xe and N₂ to facilitate the formation and break-up of the transient van der Waals molecules.^{12,25} Although the two-body and three-body terms are additive, they can be difficult to disentangle;^{12,26–30} the pressure dependence will generally result in the binary term exceeding the vdW contribution with Xe pressures greater than a few hundred torr.¹² One can instead use a simpler notation where $\gamma_{\text{SE}} = \gamma'[\text{AM}]$, where γ' is the overall SE cross-section (or the effective per-atom SE rate).

Under steady-state conditions, Xe should sample P_{AM} throughout the cell,¹⁴ giving:

$$P_{\text{Xe}}(t = \infty) = \frac{\gamma_{\text{SE}}}{\gamma_{\text{SE}} + \Gamma_{\text{Xe}}} \cdot \langle P_{\text{AM}}(z, r) \rangle; \quad (6.6)$$

Thus, for long SEOP times P_{Xe} is determined by $\langle P_{\text{AM}}(z, r) \rangle$, along with the size of γ_{SE} relative to Γ_{Xe} .

6.2.3 ¹²⁹Xe SEOP: Some Experimental Considerations

The basic aspects of SEOP instrumentation have been reviewed previously,³¹ and only a brief discussion is provided here. SEOP setups come in many forms (*e.g.* ref. 13, 17, 18, 24 and 30–48), but may generally be defined by how the gas is delivered to/from the OP cell. For example, in ‘batch-mode’ or ‘stopped-flow’ SEOP, gas loading, hyperpolarization, and transfer are separate steps. In ‘continuous-flow’ or ‘recirculating-flow’ setups, an uninterrupted supply of the gas mixture passes through the cell and is hyperpolarized during its average residence time before leaving the cell to be cryo-collected, flowed to a sample of interest, or re-directed back into the polariser. This Chapter concerns stopped-flow ¹²⁹Xe hyperpolarization under conditions of high Xe densities (~50–2000 Torr partial pressure). Other gases may be routinely added to the cell; for example, He is often used to collisionally broaden the AM line, and N₂ efficiently de-excites the Rb vapour non-radiatively *via* collisions (by absorbing the excess energy into its rovibrational degrees of freedom)—thereby suppressing the unwanted re-emission/re-absorption of omni-directional, unpolarised but resonant fluorescence photons that would otherwise occur (*i.e.* radiation trapping¹⁷).

Next, a number of different light sources have been used to generate HP gases, including diode lasers, dye lasers, Ti:sapphire lasers, and laser-diode arrays (LDAs) (*e.g.* ref. 13, 17, 18, 31–33, 35, 45 and 49–53). Because of the intrinsic advantages of LDAs—including high output power, low costs, and simple design—these devices have become increasingly dominant. However, the quality of the emitted laser light is generally poor. The broad spectral output (~2–3 nm) generally results in low absorption efficiency, necessitating high incident powers—potentially presenting thermal-management problems (from having to rely on increased cell temperatures to provide greater AM optical density and hence absorption of the laser’s spectral wings, to increased absorption by the cell’s walls, to how one manages the

heat output of the laser itself). Moreover, while the low efficiency can be partially mitigated by collision-broadening the absorption line with higher gas pressures (increasing the linewidth by $\sim 0.04 \text{ nm atm}^{-1}$),^{54,55} this practice often brings on its own complications. Finally, any absorption in the far (blue) wings of the Rb absorption line from broadband lasers may lead to inefficient pumping because of breakdown of the angular momentum selection rules owing to D_1/D_2 states-mixing.⁵⁶ Two methods have been developed that can significantly reduce the LDA bandwidth: external cavity narrowing (*e.g.* ref. 57) and volume holographic grating (VHG) narrowing—of relevance here. VHG-LDA devices can provide order-of-magnitude narrowing of LDA output with high efficiency, great ease of operation, and low cost.

In many of these lasers, the VHG is a separate optic—a slab of photo-sensitive glass containing Bragg planes of varying index of refraction. As shown in Figure 6.2(a), a narrow band of the laser emission is retro-reflected by the VHG back into the individual LDA elements, forcing them to lase at that wavelength.⁵¹ Such “fixed-frequency” VHG-LDAs can exhibit poor tunability.⁵¹ In recent designs, the VHG elements are embedded inside each diode bar. These “on-chip” VHG-LDAs exhibit improved tunability, with a $\sim 1.5 \text{ nm}$ range (often with more uniform output; Figure 6.2(b)).⁵²

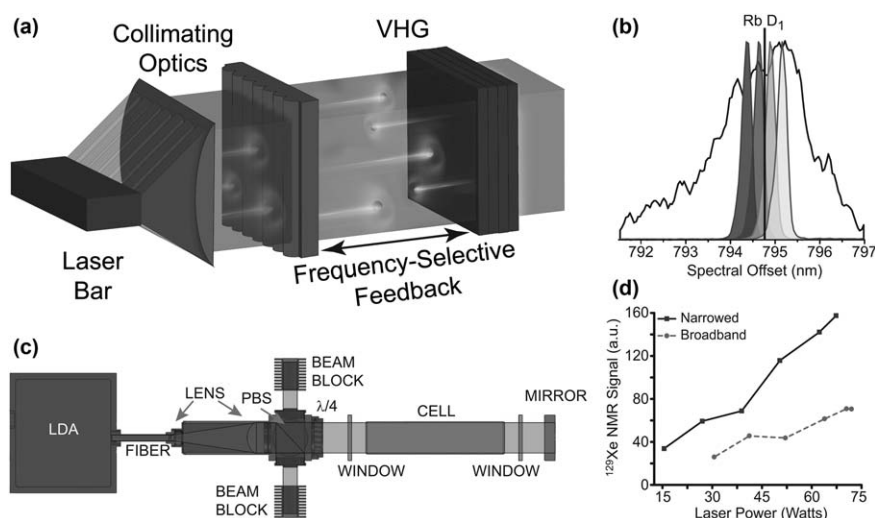


Figure 6.2 (a) Key components of VHG-narrowed LDAs. (b) Output spectrum from a broadband LDA (white) normalised in comparison to examples from a frequency-narrowed ‘on-chip’ VHG-LDA tuned to different wavelengths (grey).⁵² (c) Principal elements of the optical path for the “open-source” Xe hyperpolarizer described in Section 6.5.1.⁴⁴ (d) Comparison of low-field HP ¹²⁹Xe NMR signal (2000 Torr Xe) as a function of laser power for ‘on-chip’ VHG-narrowed *versus* broadband LDAs. Figures (b and d) adapted from ref. 52.

The design from our collaboration's open-source clinical-scale hyperpolarizer is shown as an example in Figure 6.2(c). Once the laser's output is expanded, collimated, and rendered circularly polarised, the beam is directed to the OP cell, then retro-reflected to provide a second pass, and finally directed into a beam stop. We typically observe a ~ 2 – 3 fold improvement in a watt-for-watt comparison of VHG-narrowed LDAs *versus* conventional broad-band LDAs (Figure 6.2(d)).^{30,51,52}

6.3 Exploring SEOP at High $[\text{Xe}]$ and $[h\nu]$

6.3.1 Interdependence of the Xenon Density and the Optimal SEOP Temperature

The advent of high power (20–60 W) VHG-narrowed LDAs allowed our collaboration to better explore SEOP in the regimes of high xenon densities and resonant laser flux. Initial efforts utilizing “fixed-frequency” VHG-LDAs⁵¹ found an up-to three-fold improvement in P_{Xe} compared to our initial setup^{38,39}—including $P_{\text{Xe}} > 10\%$ with 1000 Torr Xe.

Based on the relationships in the previous section, a smooth and monotonic decrease in P_{Xe} with rising Xe density ($[\text{Xe}]_{\text{cell}}$) was expected due to P_{Rb} losses from increasing Rb/Xe collisions²⁴—as well as any reductions in the SE rate because of the dwindling contribution from three-body interactions—making it more difficult to create large quantities of HPXe with high polarization. However, we observed⁵¹ a different trend where P_{Xe} initially *rose* with $[\text{Xe}]_{\text{cell}}$, *peaked* (at ~ 300 Torr), and then decreased but remained uncharacteristically high at elevated Xe pressures (~ 1000 Torr). Additionally, the P_{Xe} results were shown to be laser-power limited. Finally, it was shown that the best results were obtained with the laser detuned slightly, $\sim (-)0.11$ nm from the nominal D_1 line.

The integration of low-field ^{129}Xe NMR into the apparatus permitted *in situ* measurements of P_{Xe} as a function of $[\text{Xe}]_{\text{cell}}$, $[\text{N}_2]_{\text{cell}}$, and T_{cell} .³⁰ These experiments found a sensitive, unexpected inverse relationship between the temperature at which peak ^{129}Xe NMR signal was achieved (T_{OPT}) and $[\text{Xe}]_{\text{cell}}$, where higher cell temperatures are favored for lower Xe densities—and *vice versa* (Figure 6.3a). Little effect was observed when $[\text{N}_2]$ or total pressure was varied. These results partially explained the strange trend mentioned in the previous paragraph (those data were taken at a low constant T_{cell} , favoring higher $[\text{Xe}]_{\text{cell}}$). To gain a greater understanding of the origins of the interplay between T_{OPT} and $[\text{Xe}]_{\text{cell}}$, *in situ* NMR was used to probe P_{Xe} dynamics in real time (Figure 6.3c). Quantification of the SEOP kinetics allowed the calculation of a SEOP efficiency parameter ‘ ϵ ’ that is proportional to $\langle P_{\text{Rb}} \rangle_{\text{SE}}$; these results reproduced the interplay between T_{OPT} and $[\text{Xe}]_{\text{cell}}$ and thus showed it was independent of relaxation (Γ_{Xe}), but other aspects of the origin of the effect were poorly understood.

Nevertheless, we exploited the benefits of performing SEOP at each $[\text{Xe}]_{\text{cell}}$'s optimal temperature to achieve high P_{Xe} values over a wide range of

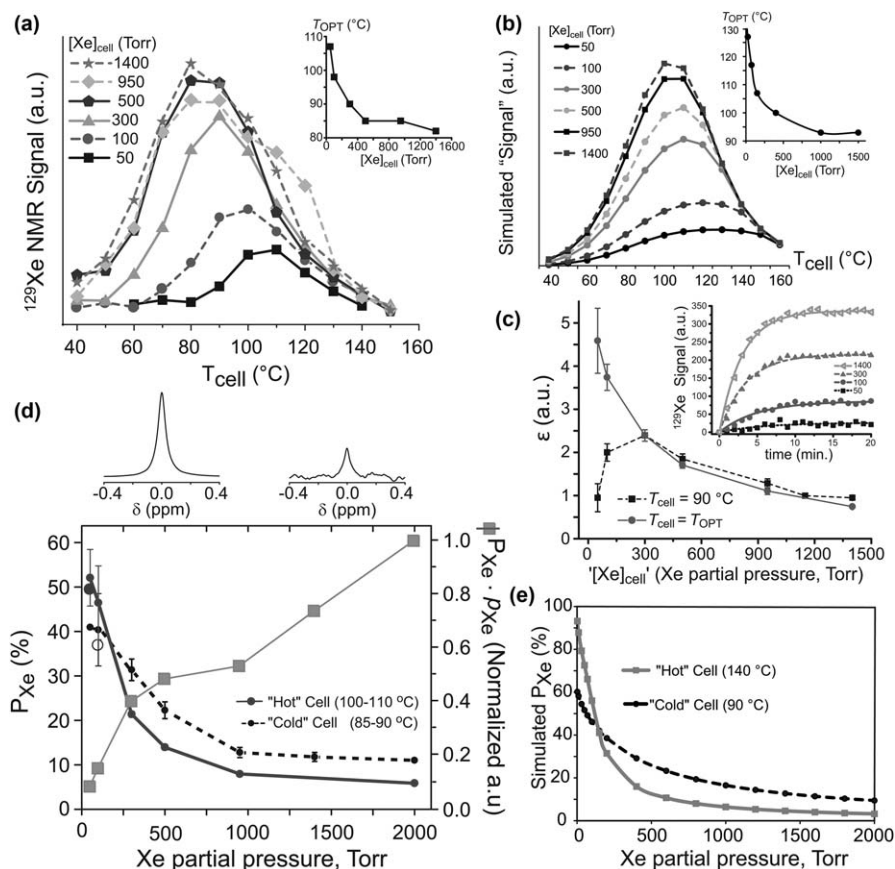


Figure 6.3 (a) ^{129}Xe NMR signal intensity ($\propto [\text{Xe}] \cdot P_{\text{Xe}}$) vs. cell temperature for six Xe partial pressures.³⁰ Inset: T_{OPT} vs. $[\text{Xe}]_{\text{cell}}$. (b) Results of simulations corresponding to data in (a). (c) Plots of an efficiency factor $\varepsilon \propto \langle P_{\text{Rb}} \rangle \gamma_{\text{SE}}$ versus P_{Xe} ; data were obtained at $T_{\text{cell}} = 90^{\circ}$ (squares) and $T_{\text{cell}} = T_{\text{OPT}}$ (circles). Inset: Time dependence of the *in situ* ^{129}Xe NMR signal during SEOP for various P_{Xe} ($T_{\text{cell}} = 90^{\circ}$).³⁰ (d) Left axis: plots of P_{Xe} measured at 9.4 T for various P_{Xe} : 'hot' (100–110 $^{\circ}\text{C}$; grey/solid line), and 'cool' (85–90 $^{\circ}\text{C}$; black/dotted line). Right axis: normalised HP ^{129}Xe NMR signal intensities for each P_{Xe} under optimal conditions. Top: comparison of HP (left) and thermal (right) ^{129}Xe NMR signals at 9.4 T, corresponding to $P_{\text{Xe}} \approx 39\%$ ($\sim 42\,900$ -fold enhancement). (e) Results of simulations corresponding to the P_{Xe} data in (d).

Figures (a, c, and d) adapted from N. Whiting *et al.*, *J. Magn. Reson.*, 2011, 208, 298–304. Copyright 2011, with permission from Elsevier.³⁰

Xe partial pressures (50–2000 torr) and with "only" ~ 29 W of (narrowed) laser power.³⁰ Following transfer of the gas samples to high field (9.4 T), NMR measurements yielded average P_{Xe} values of $\sim 52\%$, $\sim 32\%$, $\sim 23\%$, and $\sim 11\%$ at 50, 300, 500, and 2000 Torr Xe, respectively (Figure 6.3d)—at the time, the highest P_{Xe} values attained at such high $[\text{Xe}]_{\text{cell}}$ (~ 0.06 to ~ 2.5

amagat) in such large cells (*cf.* ref. 18, 32 and 58). Additionally, at higher $[\text{Xe}]_{\text{cell}}$ values, P_{Xe} leveled off instead of falling dramatically—meaning that the total magnetization (and hence MR signal) actually grew as $[\text{Xe}]_{\text{cell}}$ increased—counter to original expectation. Finally, the qualitative trends predicted by the data in Figure 6.3a and c are manifested in Figure 6.3d, with higher P_{Xe} values observed at lower cell temperatures for higher $[\text{Xe}]_{\text{cell}}$, and *vice versa*.

6.3.2 Simulations of the $[\text{Xe}] - T_{\text{OPT}}$ Dependence

To better understand the origin of trends between experimental SEOP parameters and P_{Xe} , we performed a series of Mathematica-based simulations.⁸⁷ These simulations were based on iterative calculations for photon flux dependent on local P_{Rb} , while assuming symmetric laser and Rb cross-section frequency distributions, as well as single average values to represent global cell temperature and the (spatially averaged) xenon polarization—a product of the simulation.

Considering only the level of physical relationships presented in Section 6.2, the simulation quantitatively recaptured much of the inverse relationship between T_{OPT} and $[\text{Xe}]_{\text{cell}}$ (Figure 6.3b). The effect arises primarily from the Xe–Rb spin-rotation interaction that drives Γ_{SD} : higher xenon fractions are accompanied by higher rubidium spin-destruction rates,^{19,20} which depolarises the Rb vapour—and in turn, causes greater cell opacity and thus poor illumination. Particularly in the limit where the (Rb-independent) ^{129}Xe spin-relaxation rate is negligible, the effects of the greater Xe-induced Rb spin-relaxation can be mitigated by reducing the cell temperature—and hence $[\text{Rb}]$ —to maximise photon flux throughout the cell. In this way, raising the “photon-to-Rb ratio” by reducing T_{cell} when $[\text{Xe}]_{\text{cell}}$ is high, albeit at the expense of reducing γ_{SE} , can increase $\langle P_{\text{Rb}} \rangle$ and hence P_{Xe} . This effect is also seen in the simulated and realised ^{129}Xe polarization values plotted in Figure 6.3(d and e).

The simulations also predict that the $T_{\text{OPT}}/[\text{Xe}]$ effect should diminish as the laser’s bandwidth is increased (independent of total laser power). This dependence may be explained by the fact that broadband lasers have a greater number of quasi-resonant photons in the spectral wings that can help mitigate the otherwise poor illumination in optically dense cells. Indeed, we have seen the effect minimised with broadband lasers.⁵³ Not all effects are reproduced by the simulations, which did not include some gas-dependent changes to the Rb absorption profile,⁵⁴ ultra-high gas temperatures from quenched radiation trapping (see Section 6.4), and convection,⁵⁹ among others. For example, the simulations do not predict the steep fall-off in P_{Xe} at higher temperatures observed experimentally (likely reflecting the absence of “Rb runaway”,^{33,48,52,59,60,62}/feedback mechanisms in the Rb density); additionally, this model did not exhibit the experimentally observed anomaly of higher P_{Xe} for higher xenon fractions under some conditions.^{30,51}

6.3.3 Interplay between Xenon Density and Laser Centroid Wavelength

Access to high power, *tunable* frequency-narrowed laser sources allowed the study of the effects of resonant laser flux, spectral offset, T_{cell} , and $[\text{Xe}]_{\text{cell}}$ on P_{Xe} .⁵² For example, we observed an unexpected interplay between $[\text{Xe}]_{\text{cell}}$ and the dependence of P_{Xe} on laser offset—manifested by an asymmetric (‘red’-sided) broadening of the P_{Xe} wavelength dependence (and corresponding Rb D_1 laser-absorbance) upon increased $[\text{Xe}]_{\text{cell}}$ (Figure 6.4(a,b)): peak P_{Xe} values for high Xe densities are attained with increased (‘red’-sided) spectral offset and lower cell temperatures. Moreover, as the cell temperature is increased, the overall ^{129}Xe signal decreases and the locally optimal P_{Xe} (for that T_{cell}) is achieved at increasingly blue- and red-shifted wavelengths with a widening and highly bifurcated P_{Xe} profile (Figure 6.4(a)). Increased temperatures also

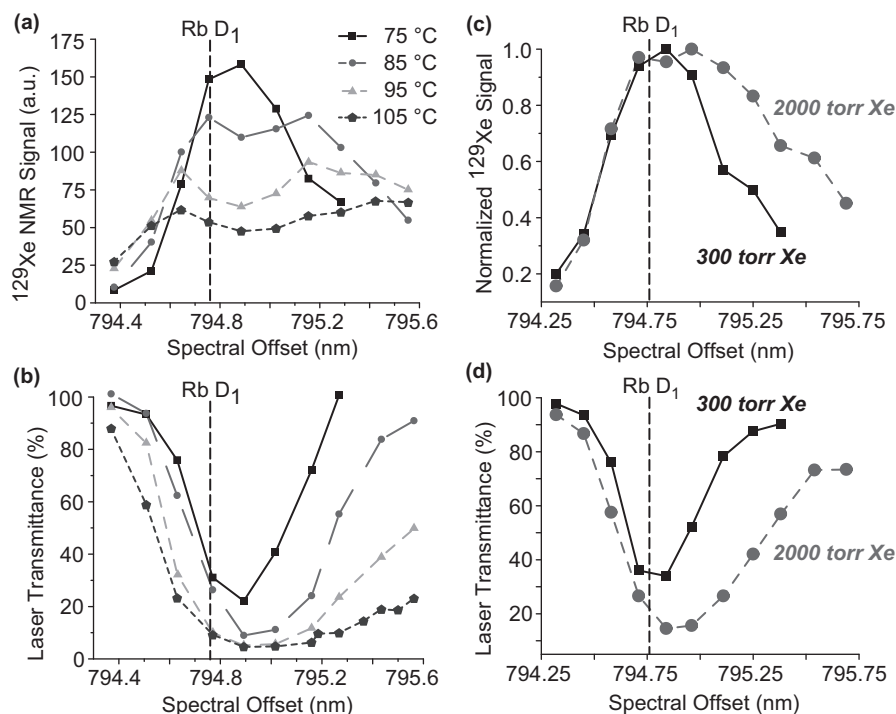


Figure 6.4 (a) Low-field ^{129}Xe NMR signal vs. laser wavelength for various T_{cell} . (b) Corresponding laser transmittance. OP conditions: 2000/600 torr Xe/ N_2 ; ~ 63 W laser. (c) Low-field HP ^{129}Xe signal vs. laser wavelength: 300/1700 torr Xe/ N_2 (solid) and 2000/600 torr Xe/ N_2 (dashed). Prior to normalization, each value was divided by the laser power (to correct for any power variations with different LDA temperatures). (d) Laser transmittance. OP conditions: $T_{\text{cell}} = 85$ °C; ~ 63 W laser. Figures adapted from ref. 52.

resulted in correspondingly deepened absorption profiles that were asymmetrically broadened to the ‘red’-side of the Rb D_1 (Figure 6.4(b)).

The bifurcation observed in Figure 6.4(a) likely explains the previously mentioned observation⁵¹ of higher P_{Xe} values with a blue-shifted LDA frequency offset, as in retrospect those experiments were performed with cell temperatures above the optimal values (and red-shifting much beyond the nominal Rb D_1 line was not possible)—as well as qualitatively similar results in ref. 61. In another example, this wavelength-dependent effect was further studied at two Xe gas densities (300/1700 and 2000/600 Torr Xe/N₂) at fixed $T_{\text{cell}} = 85^\circ\text{C}$, where performing SEOP at the higher [Xe] value resulted in significant red-shifting and asymmetric broadening of the optimal P_{Xe} and laser-absorption profiles (Figure 6.4(c,d)).

The complex dependence of ^{129}Xe polarization on OP laser wavelength⁵² appears to result from two contributions: (1) the interplay between cell illumination (better with lower [Rb] and/or higher $\langle P_{\text{Rb}} \rangle$) and the SE rate ($\propto [\text{Rb}]$); and (2) [Xe]-dependent changes to the Rb absorption line.^{54,55,62–64} These [Xe]-dependent changes—including shifting and asymmetric broadening of the Rb D_1 line—are qualitatively similar to what is expected based on a vdW model,^{54,62–64} but are significantly greater in magnitude. For instance, for a cell with 2000/600 Torr Xe/N₂ gas loading, one would expect to see a linewidth and red-shift of only ~ 0.12 and ~ 0.039 nm, respectively. However, we observed an effective linewidth of ~ 0.31 nm and a red shift of up to ~ 0.25 nm. Within the vdW model, a slight ($\propto T^{0.3}$)⁵⁴ temperature dependence is expected for these lineshape parameters—suggesting that greatly elevated internal cell temperatures could be involved (see Section 6.4.2). However, deviations from the van der Waals model—including [Xe]-dependent contributions to the Rb absorption profile from a red-side satellite line resulting from the Rb/Xe interatomic potential—may also play a role.⁵⁴ Finally, the results of this section demonstrate the importance of global, independent optimization of the many experimental parameters governing SEOP—not only to learn about underlying phenomena, but also to determine the best practices for generating HP gases for a given application.

6.4 Studies of Energy Emission, Transport, and Dissipation during SEOP at High [Xe] and $[h\nu]$

6.4.1 Characterization of Visible Emission from Rb OP Cells

Only a miniscule fraction of the photon energy that enters the OP cell goes into flipping electronic (and ultimately, nuclear) spins—the rest of the energy must leave the excited Rb atoms as either *light* or *heat*. For example, one early set of experiments using the original setup at SIUC involved the investigation of *visible* light emission—strikingly bright violet light—from Rb cells under a range of conditions relevant to SEOP,³⁹ particularly under non-optimal conditions. Recording the emission spectra under various conditions (Figure 6.5a) found that the primary emission at ~ 421 nm (“3”,

$6P \rightarrow 5S$) was consistent with energy-pooling processes⁶⁵ of the type: $\text{Rb}^*(5P_{1/2}) + \text{Rb}^*(5P_{1/2,3/2}) \rightarrow \text{Rb}^*(6P_{1/2,3/2}) + \text{Rb}(5S_{1/2})$, similar to effects explored by Walker.^{66,67}

Energy pooling involves the through-space, non-radiative transfer of energy between two nearby excited species resulting in one species residing in a higher excited state, and leaving the other in the ground state. The 421 nm emission exhibits a classic quadratic dependence upon both the incident resonant laser power (Figure 6.5b inset) and the emission at 780 nm ($\propto [\text{Rb}]^*$). All lines observed were assignable to neutral, monoatomic Rb⁶⁸—indicating Rb* population up to $\geq 9D$ ($\sim 31\,220\text{ cm}^{-1}$). Such energies exceed those required for production of laser-induced plasma,^{65,69,70} the formation of which would be consistent with the observation of a white-light baseline.⁷⁰ As an aside, spectral signatures for Rb₂ dimers at ~ 600 – 605 and ~ 680 – 720 nm ^{71,72} were not seen under these relatively mild conditions. Dimers and larger Rb clusters—recently hypothesised to be negatively affecting Xe polarization in some circumstances⁸⁸ may still be possible under higher-temperature, higher laser-power conditions in continuous-flow polarisers.

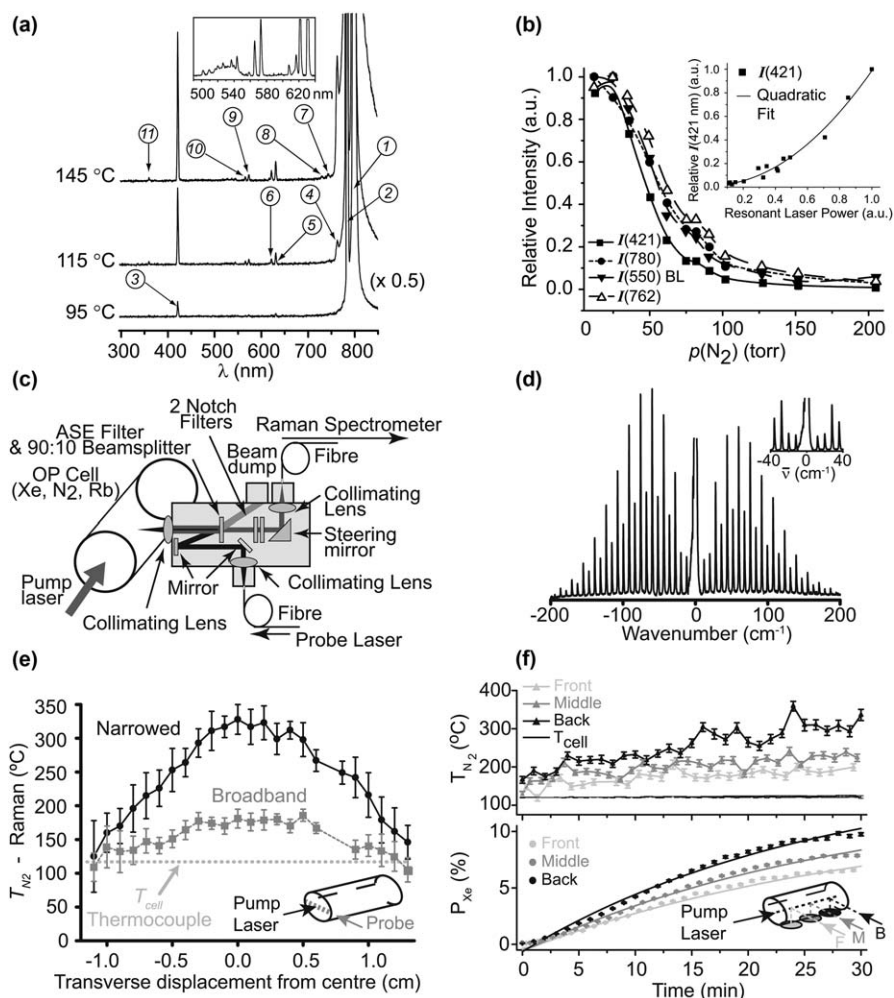
Although the visible emission increases rapidly with cell temperature (consistent with the exponential dependence of the Rb vapour pressure), the emission falls steeply with increasing partial pressure of nitrogen (Figure 6.5b). N₂ gas has long been added as a buffer gas to quench radiation trapping—involving the re-emission and reabsorption of resonant but omnidirectional and unpolarised light. Indeed, the negative effects of radiation trapping for generating high spin polarization are well-established;^{13,17} it is expected that the 421 nm emission is not, in itself, particularly detrimental to OP compared to near-IR fluorescence at the *D* lines. Instead, violet emission can provide a sensitive, background-free indicator of unwanted radiation-trapping processes, and could prove useful when optimizing the OP gas mixture; for example, we have since used at least 200 Torr N₂ in virtually all of our subsequent SEOP experiments. On the other hand, the presence of laser-induced plasma is unlikely to be helpful (possibly leading to damaged cell coatings and seals over time).

6.4.2 Probing Energy Thermalization Processes During Xe SEOP with *In Situ* N₂ Rotational Raman Spectroscopy

The SEOP process is dependent on many parameters, such as gas mix, laser power and wavelength, and oven temperature. However, the oven temperature is often not a true reflection of the internal gas temperature. Recently, we have investigated the effects of energy thermalization processes where light is *not* emitted—*i.e.*, where sufficient molecular N₂ is present to collisionally de-excite the Rb. However, these processes result in the accumulation of large amounts of energy in the rovibrational degrees of freedom of N₂. This energy may be thermally distributed to other species throughout the

cell in a heterogeneous fashion, and eventually dissipated to the cell walls and surroundings. In studies of helium-rich OP cells, Walter *et al.*⁷³ used rotational Raman spectroscopy of N₂ to show that the internal gas temperatures could be elevated above the oven temperatures, denoted as T_{cell} , by up to 200 °C.

It is important to have knowledge of internal gas temperatures as they may affect many spin exchange and spin destruction terms—due both to intrinsic dependencies as well as the larger effects resulting from elevated temperatures creating higher alkali metal densities. Given the much greater spin-destruction rate with Xe (and the much lower gas thermal conductivity), there could be greater risk of complications with higher Xe densities. In one set of experiments studying Xe SEOP at high [Xe] and $[h\nu]$, we utilised an orthogonal Raman excitation/read-out geometry (as utilised by Walter *et al.*⁷⁵)



to probe internal gas temperatures during SEOP.⁷⁴ Dramatically elevated gas temperatures are reported—up to ~ 1000 K for OP cells with ~ 400 K exterior temperatures—with the highest values observed with increased laser powers, red-shifting of the OP laser from the nominal Rb D_1 transition wavelength, longer SEOP times, and higher Xe/N₂ ratios. These high temperatures are still too low for the observed line shape distortions to be consistent with a simple vdW interactomic potential model.^{52,54} This work also showed how the Raman approach could be useful to study the interplay of Xe density, polarization, alkali metal density, and in-cell temperature over time—providing the first indirect evidence that reduced thermal conductivity of Xe compared to lighter gases may be a contributing factor in greater thermal management issues at higher Xe densities.

The orthogonal arrangement in the above work suffers from sensitivity issues; moreover, achieving satisfactory alignment and background subtraction is tedious. Utilising a new in-line module for excitation and detection of the Raman scattering (Figure 6.5c), where optical filters are used to suppress Rayleigh scattering, a ≈ 23 fold improvement in signal-to-noise ratio (SNR) of the Raman peaks was observed⁶³ relative to a conventional orthogonal set-up. This SNR improvement allows real-time monitoring of the energy transport processes *in situ* within an optical pumping vessel. By probing the ultra-low frequency Raman scattering of the N₂ gas (Figure 6.5d), a rotational temperature of the gas, T_{N_2} , is calculated (which reflects the gas temperature at a given location within the cell⁷³). The capability of this apparatus was recently demonstrated when we explored the position-dependent variation in internal gas temperature obtained with frequency-narrowed *versus* broadband LDAs (Figure 6.5e). Temperatures were raised

Figure 6.5 (a) Temperature dependence of visible emission lines from a Rb OP cell with 300 Torr Xe and ~ 33 W broadband laser: “1” and “2”: $5P \rightarrow 5S$ (D_1 & D_2); “3”: $6P \rightarrow 5S$; “4”: $5D \rightarrow 5P$; “5”&“6” $6D \rightarrow 5P$; see also ref. 39. The *inset* shows 590–640 nm region with a longer integration time under similar conditions (141 °C, 300 Torr Xe, ~ 10 torr N₂). (b) Relative intensities of visible emission lines at 421, 780, and 762 nm as functions of N₂ pressure at 140 °C and 300 torr Xe (curve for 550 nm is for the baseline, “BL”). Inset shows the quadratic dependence of the 421 nm line. Adapted from I. Saha *et al.*, *Chem. Phys. Lett.*, 2006, **428**, 268–276. Copyright 2006, with permission from Elsevier. (c) Schematic of the *in situ* Raman/SEOP apparatus featuring the in-line module. (d) Typical Raman spectrum for measuring N₂ temperatures. Inset: resolvable ultra-low frequency Raman peaks.⁶⁵ (e) Comparison of internal gas temperatures, T_{N_2} , relative to T_{cell} (dotted line) perpendicular to the pump laser (inset), for a 60 W, 2.13 nm FWHM broadband LDA (squares) and a 60 W, 0.26 nm FWHM frequency-narrowed LDA (black circles) with 100/1900 Torr Xe/N₂. The centre of the cell is shown to be vastly elevated in temperature (T_{N_2}) compared to the wall temperature, which is shown to be equal to the oven temperature, T_{cell} . (f) ^{129}Xe polarization and T_{N_2} build up shown at front, middle and back of an OP cell (inset) with 1500/500 torr Xe/N₂ at 120 °C, using a 60 W frequency-narrowed laser.

above T_{cell} by $\sim 40^\circ\text{C}$ for the broadband LDA, compared to $\sim 200^\circ\text{C}$ for the VHГ-narrowed LDA with just 5 min of SEOP—reflecting the increase in resonant photon flux. The decreased temperatures observed in the broadband LDA experiments are attributed to the spectral wings of the LDA being absorbed less compared to the narrowed source. Figure 6.5e also shows the dependence of T_{N_2} perpendicular to the main pump beam—illustrating that the oven temperature (dotted line) is essentially equal to the wall temperature, and that a substantial increase in gas temperature is observed towards to the centre of the cell.

We are currently using the in-line Raman setup to study the energy dissipation during SEOP at high $[\text{Xe}]$ and $[h\nu]$ in greater detail. For example, when SEOP is stable under ostensibly “steady-state” conditions, P_{Xe} and internal gas temperatures can increase concomitantly when monitored as functions of time and spatial position within the OP cell (Figure 6.5f).⁸⁹ It is thought that the cell wall temperature (T_{cell}) initially governs $[\text{Rb}]$ even though the gas temperatures in the centre can be vastly elevated from this value. For this reason and because the gas flow from the oven’s heater enters near the rear of the cell, P_{Xe} and T_{N_2} are generally greatest at the back, with the temperatures elevated by hundreds of degrees relative to thermocouple measurement. The temperature gradient across the optical pumping vessel is expected to create a Rb number density gradient (and possibly Rb polarization gradients as well)—resulting in an apparent P_{Xe} gradient across the length of the vessel ($l_{\text{cell}} = 167\text{ mm}$, $r_{\text{cell}} = 20\text{ mm}$) that appears to remain despite expected convection of the Xe gas. Higher oven temperatures and laser powers, however, can lead to a larger temperature gradient across the cell, “Rb runaway”,^{33,48,52,60} poorer P_{Xe} , and unstable SEOP—and we expect this powerful *in situ* capability to provide new insights into such phenomena.

6.5 Clinical-scale Stopped-flow Xe “Hyperpolarizers”

6.5.1 The “XeNA” Hyperpolarizer

Over the last two decades a considerable amount of work has investigated the use of HP noble gases for biomedical and clinical applications (for reviews, see ref. 31 and 75–77 as well as other chapters here). The efforts described in the previous sections of this chapter provided considerable knowledge concerning stopped-flow SEOP under conditions of high xenon densities and photon fluxes. ^{129}Xe polarizations that resulted from this work were tantalizingly high, but the production scale was relatively small. Encouraged by these promising results, our SIUC/Nottingham collaboration expanded to include groups at Vanderbilt (led by E.Y.C.), Harvard/MGH (led by Matthew Rosen) and Harvard/B&WH (led by Sam Patz)—with the goal of significantly “scaling up” these approaches to create an automated, self-contained “hyperpolarizer” that could be used for human studies in clinical settings.

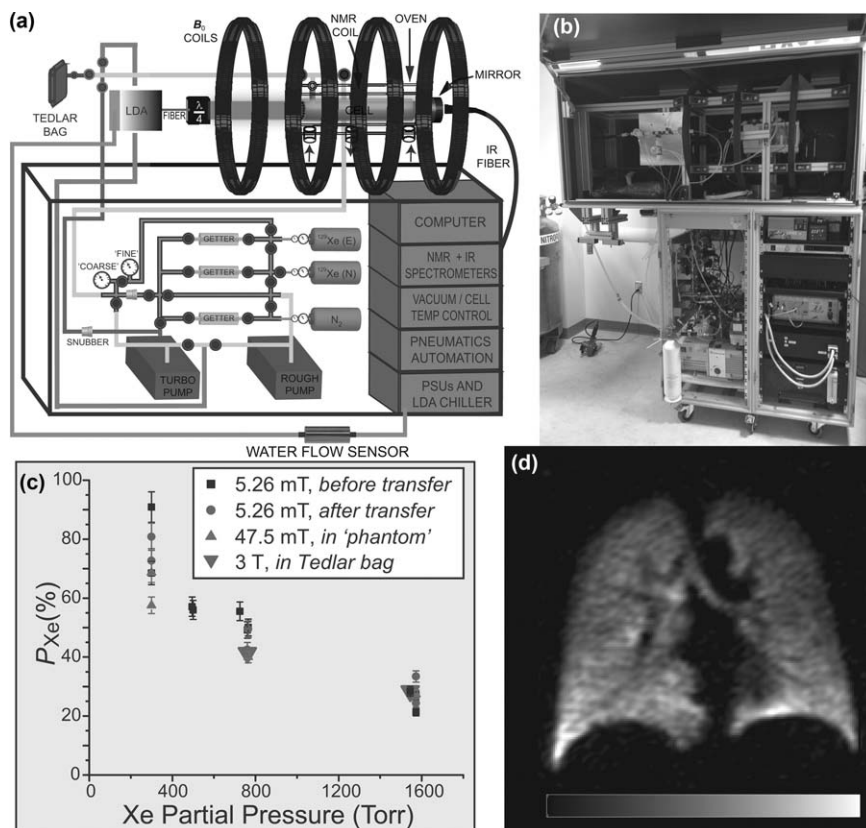


Figure 6.6 (a) XeNA hyperpolarizer schematic. (b) Corresponding photo. (c) ¹²⁹Xe nuclear spin polarization values measured at 5.26 mT (*in situ*), 47.5 mT (*ex situ*), and/or 3 T (*ex situ*), versus xenon partial pressure determined at loading. ‘Before’ and ‘after transfer’ labels are with respect to when gas was transferred from the cell to another container. For most data, ~170 W was incident on the cell, of which ~90 W was absorbed. (d) Slice from a 3D HP ¹²⁹Xe gradient echo chest image from a healthy human subject.

Figures (a and b) adapted from P. Nikolaou, *et al.*, *Magn. Reson. Imag.*, 2014, 32, 541–550. Copyright 2014, with permission from Elsevier.⁴⁵

Figures (c and d) adapted from ref. 44.

Our first-generation hyperpolarizer, dubbed “XeNA”^{44,45} (Xenon polarization Automated) was designed, constructed and installed in 2010–2012 (Figure 6.6(a and b)). XeNA was developed using an ‘open-source’ collaborative approach, where the designs and experiences of multiple labs were leveraged to take advantage of the best practices in the area of batch-mode ¹²⁹Xe SEOP; all aspects of the design and operation are shared with the community. Indeed, wherever possible most components are commercially available—even the OP cells—in order to help others replicate and improve upon this platform.

XeNA consists of several key components contained in one chassis: (i) 200 W frequency-narrowed LDA, (ii) vacuum pump system, (iii) NMR and IR spectrometers reporting on ^{129}Xe hyperpolarization and laser light transmittance, (iv) gas-handling manifold for OP-cell loading and expanding the HP $^{129}\text{Xe}/\text{N}_2$ gas mixture into ~ 1 L Tedlar bag, (v) B_0 electromagnet (four ~ 24 in. ID coils generating 5.26 mT), (vi) controller box (the brain of the hyperpolarizer), and (vii) OP-oven containing the OP-cell (~ 0.5 L volume). The OP-oven temperature is maintained by heaters and a gas supply from a self-pressurised liquid N_2 dewar. Operations are performed in automated fashion where the operator uses a graphical user interface (GUI) to run specific tasks of the HPXe production cycle. The OP-cell can be loaded automatically with a desired mixture (naturally-abundant or isotopically enriched) ^{129}Xe and N_2 . Once the desired ^{129}Xe hyperpolarization is achieved, the OP-oven is rapidly cooled to $<40^\circ\text{C}$ to reduce the Rb gas-phase concentration prior to transfer.

The results summarizing the performance of the XeNA hyperpolarizer are provided in Figure 6.6(c and d). The following in-cell P_{Xe} values were obtained: $90.9 \pm 5.2\%$, $57.1 \pm 3.3\%$, $50.1 \pm 2.9\%$, and $33.4 \pm 1.9\%$ measured for Xe loadings of 300, 495, 765, and 1570 Torr, respectively (Figure 6.6c).^{44,45} Although XeNA has the ability to cryo-collect HPXe, the combinations of such high Xe fractions and polarizations makes cryo-collection unnecessary (see also ref. 40 and 41)—greatly simplifying the operation of the polariser. We note that without cryo-collection, the HP ^{129}Xe is diluted somewhat by the N_2 gas present, but is otherwise safe to administer. The HP gas mixture is allowed to expand into a previously evacuated and purged ~ 1 L Tedlar bag *via* a filter (Rb “getter”). Approximately 0.8 L of Xe: N_2 gas mixture is obtained in one production cycle lasting ~ 35 – 40 minutes (after expansion of the OP-cell’s contents given a typical total pressure at loading of ~ 2000 Torr). The lifetime of the HP state is long in the Tedlar bags, up to ~ 5.9 h at 3 T. The following P_{Xe} values were obtained following transport to a 3 T MRI: $41 \pm 1.6\%$ and $28 \pm 1.1\%$ with Xe in-bag mole percentages of 38% and 77% respectively.

While the hyperpolarizer operator performs most of the operations *via* GUI, some operations were not automated, including those involving the liquid N_2 dewar, probing P_{Xe} *in situ*, and LDA adjustment. Moreover, the entire procedure is divided into several steps instead of a single “push-button” operation. Nevertheless, the level of XeNA automation significantly minimises operator’s involvement and human error. Following XeNA’s installation in the laboratory of Prof. Samuel Patz at B&WH in 2012, XeNA received FDA clearance for use in a clinical COPD trial. An example of ^{129}Xe MRI performed using HPXe produced by XeNA is shown in Figure 6.6(d).^{44,45}

6.5.2 The “XeUS” Hyperpolarizer

Our second-generation batch-mode clinical hyperpolarizer, dubbed “XeUS” (for Xenon Ultimate Spin exchange)^{46,62} was developed and constructed

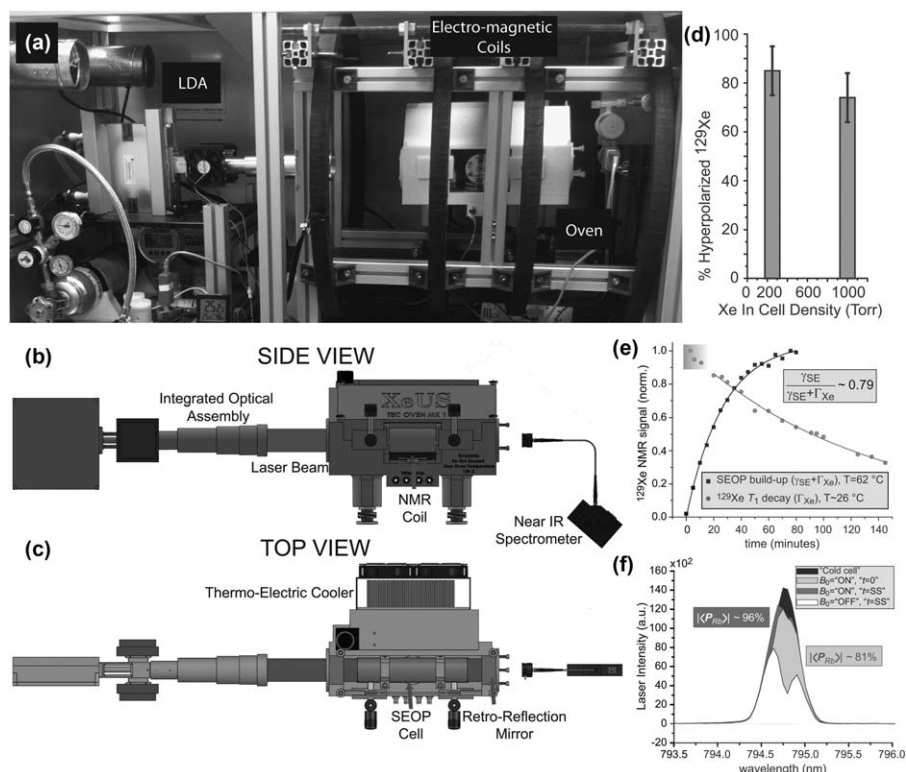


Figure 6.7 (a) Photograph of XeUS upper frame; (b) and (c) are side- and top-view schematics of LDA with integrated optical assembly, TEC OP-oven with OP-cell, and near-IR spectrometer. (d) Bar graph of $\%P_{\text{Xe}}(\text{max})$ of 250 and 1000 Torr Xe cells. (e) Time-dependent *in situ* HP ^{129}Xe build up (black) and T_1 relaxation (grey) in an OP-cell filled with 1000/1000 torr Xe/N₂. (f) Field-cycled, near-IR spectra of transmitted laser used to estimate $|\langle P_{\text{Rb}} \rangle|$, obtained: (i) at room temperature (black); (ii and iii) during SEOP with B_0 on at T_{OPT} (here 62°C) at $t=0$ (light grey) and at steady state (dark grey); (iv) at steady state with B_0 off (white). $|\langle P_{\text{Rb}} \rangle|$ is estimated from a ratio comparing the absorbances measured when B_0 is on *versus* off; see ref. 45 and 51.

Figures (a–c) and (d–f) adapted with permission from ref. 62 and 46 respectively. Copyright 2014 American Chemical Society.

based on experiences with the XeNA hyperpolarizer with primary objectives of (i) enhancing P_{Xe} performance, and (ii) increasing the level of automation and polariser robustness.

The overall conceptual design of XeUS (Figure 6.7(a, b, and c)) does not differ significantly from that of XeNA, but a series of technical advances was implemented,^{46,62} including: (i) A CAD-designed chassis, allowing its commercial manufacture and significant reduction in device footprint; (ii) 200 W VHGLDA with custom-designed optical chassis that expands, collimates, and circularly polarises the beam, ensures homogeneous flux throughout

the cell, and greatly facilitates alignment; (iii) a large Thermo-Electric Cooling (TEC) unit is used to control the temperature of OP-cell and oven, and is fully automated and consumes only electricity; (unlike the above XeNA hyperpolarizer that additionally requires liquid N₂ and an external source of pressurized inert gas or dry air for routine operation); (iv) The Barker magnet geometry allowed a smaller chassis, and its lower field (4.00 mT) generates less waste heat; (v) a simplified gas manifold uses a pre-mixed Xe/N₂ cylinder to supply the cell *via* a constantly pressurised line (reducing ‘dead’ time and lowering the risk of cell oxidation); (vi) the OP-cell has two ports for loading and gas expansion/transfer to the sample; moreover, the TEC’s temperature sensor is now mounted on the OP-cell directly—which, when combined with the 3D-printed oven design—provides better regulation of the OP-cell temperature to permit systematic multi-dimensional mapping of the SEOP conditions and parameter space;⁶² and (vii) The OP-oven was 3D-printed⁴⁶ to enable integration of all components including TEC module, IR/NMR spectroscopies, laser input, and retro-reflection. A copy of this oven can be printed in ~2 days. Furthermore, a 3D-printed version of the XeNA oven was developed retroactively, negating the previous disadvantages of time-consuming custom manufacture; this design can be downloaded/printed as part of the open-source solution.⁴⁶

These features combined to significantly improve device robustness, automation, and operation^{46,62}—as well as ¹²⁹Xe polarization performance. Examples of P_{Xe} build-up and decay curves are shown in Figure 6.7e that provide values for γ_{SE} and T_1 (here exceeding 2 h). Like XeNA, XeUS also allows the Rb electronic spin polarization to be estimated from changes in the transmitted laser intensity when the magnetic field is cycled (Figure 6.7f), giving values as high as $\langle P_{\text{Rb}} \rangle \sim 96\%$ in a cell containing 1000 Torr each of Xe/N₂. The corresponding value for P_{Xe} is as high as 74% (Figure 6.7d);⁴⁶ this value is in excellent agreement with the value (~76%) predicted using the right side of eqn (6.6)—and compares favorably to the interpolated value for XeNA of ~40%. As another example, at 500 Torr Xe $P_{\text{Xe}} = 57.1 \pm 3.3\%$ was attained with XeNA; for XeUS $73 \pm 4\%$ has been routinely achieved,⁶² with values now reaching 90% for this mixture (as measured by *in situ* low-field NMR polarimetry).⁶⁴ Ongoing efforts concern improving HPXe throughput by decreasing production time for individual batches while maintaining the high ¹²⁹Xe polarization.

6.6 Exploring High-[Xe] SEOP using Cesium

6.6.1 Cesium *versus* Rubidium for Hyperpolarizing ¹²⁹Xe

Despite successes with the clinical-scale hyperpolarizers, studies of fundamental aspects of SEOP under high [Xe] and $[h\nu]$ have continued—including the investigation of using cesium for ¹²⁹Xe SEOP. While any of the alkali metals may be used, rubidium has long been preferred due to its favorable SE cross-section,^{10,11,13} relatively high vapour pressure, and available

high-power, low-cost laser sources at the Rb D_1 wavelength (~ 795 nm).⁵⁰ Despite these benefits, there are potential advantages to using *cesium* for ^{129}Xe hyperpolarization: the SE cross-section for Cs/ ^{129}Xe has been measured to be ~ 1.9 -fold that of Rb/ ^{129}Xe ,^{26–28} and the estimated Cs/ ^{129}Xe spin destruction rate⁷⁸ (currently unmeasured) is predicted to be only half that of the experimentally measured Rb/ ^{129}Xe SD rate²⁰ (although the *predicted* Cs/ ^{129}Xe and Rb/ ^{129}Xe SD rates are similar in value^{20,55}). Additional benefits include even higher vapour pressures, lower-energy D line transitions,⁷⁹ and greater spacing between D lines^{55,80} (lowering the possibility of simultaneously pumping collisionally-broadened D_1 and D_2 transitions). However, despite important previous efforts (*e.g.* ref. 79, 81 and 82), the potential benefits of Cs/ ^{129}Xe SEOP had not been realised and Cs remains not as widely used—in part a consequence of the dearth of high power light sources that are resonant to the Cs D lines.

The acquisition of newly-developed broadband LDAs capable of reaching the Cs D_1 (894.3 nm), Cs D_2 (852.1 nm), and Rb D_1 (794.8 nm) lines (Figure 6.8a) allowed members of our collaboration to compare the preparation of HP ^{129}Xe with Cs and Rb on equal footing.⁵³ Because the maximum P_{AM} achievable with D_2 OP is 0.5 instead of 1 (Section 6.2), it is not as effective as D_1 SEOP, but pumping on the D_2 line can still result in appreciable P_{Xe} levels^{81,82} (in case a D_1 source is not available). Additionally, because the D_2 line possesses twice the oscillator strength,⁸³ more light is absorbed, and the optimal temperature⁵³ for Cs D_2 pumping is lower than for D_1 . As anticipated, ^{129}Xe nuclei were polarised in opposite directions for D_1 and D_2 pumping using the same light helicity (due to the 1:3 depopulation ratio)—which also illustrates the source of concern of accidentally pumping the red-side wing of the D_2 line for alkali metals with more closely spaced D lines.

The build-up of ^{129}Xe magnetization (Figure 6.8b) can be monitored *in situ* via low-field NMR and fit to eqn (6.4), yielding rate constants that can be plotted as a function of alkali metal density (estimated from vapour pressure curves⁸³) to extract the SE cross-section ($\gamma' = \gamma_{\text{SE}}/[\text{AM}]$; Figure 6.8c) and ^{129}Xe spin-destruction rate (Γ_{Xe}). Importantly, the average γ' values for Cs/ ^{129}Xe SEOP were ~ 1.5 -fold larger than for Rb/ ^{129}Xe —in good agreement with previous studies^{26–29} (Γ_{Xe} values also appeared to be lower for Cs).

Finally, high-field (9.4 T) *ex situ* NMR allowed side-by-side comparisons of Cs *vs.* Rb OP (Figure 6.8d). A ~ 2 -fold improvement in P_{Xe} was achieved using Cs—with the highest gains attained at the greatest Xe densities. Moreover, the measured P_{Xe} values closely tracked the estimated polarizations inferred for the alkali metals (using parameters in eqn (6.6)), with P_{Xe} tracking P_{Cs} more closely than P_{Rb} , and the values for P_{Rb} appearing to fall off more steeply with increasing [Xe]. Taken together, these results showed that Cs can provide improved hyperpolarization of ^{129}Xe under conditions relevant to NMR/MRI, and are consistent not only with higher γ' values and lower Γ_{Xe} values for Cs/ ^{129}Xe SEOP, but appear to support the lower predicted values for the Cs Γ_{SD} rates as well.

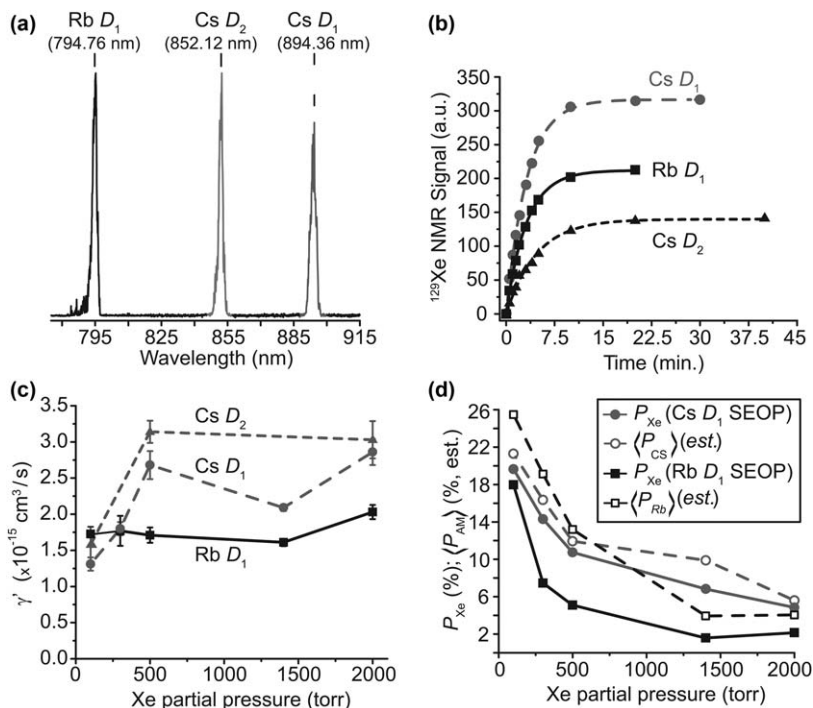


Figure 6.8 (a) Composite of three optical spectra of different broadband LDAs emitting at the Rb D_1 , Cs D_2 , and Cs D_1 transition lines, respectively (Cs $D_1 = \sim 46$ W, $\Delta\lambda_{\text{fwhm}} = 2.9$ nm; Cs $D_2 = \sim 40$ W, $\Delta\lambda_{\text{fwhm}} = 1.9$ nm; Rb $D_1 = \sim 53$ W, $\Delta\lambda_{\text{fwhm}} = 2.1$ nm). (b) Selected P_{Xe} build-up curves from Rb/ ^{129}Xe or Cs/ ^{129}Xe SEOP. (c) Plots of γ' vs. Xe partial pressure (p_{Xe}) for Rb D_1 (solid), Cs D_1 (dashed), and Cs D_2 (dotted) OP. (d) Plots of P_{Xe} vs. p_{Xe} following Cs/ ^{129}Xe (circles) or Rb/ ^{129}Xe (squares) SEOP, measured at 9.4 T. Estimates for $\langle P_{\text{AM}} \rangle$ are inferred from P_{Xe} , γ_{SE} , and Γ_{Xe} values, using eqn (6.6). Figures adapted from ref. 53.

6.6.2 Investigating Cs/Rb “Hybrid” SEOP: Initial Efforts

It is important to note that the above results showing improved P_{Xe} using Cs were achieved with *broadband* lasers.⁵³ Although technology development at Cs wavelengths has lagged that for Rb, recently there has been improvement in VHG-narrowed lasers designed to reach the Cs D_1 line (at ~ 894.3 nm). However, such lasers often struggle to tune much beyond 894.0 nm; for example, in our recent efforts using on-chip VHG-narrowed lasers,⁹⁰ the improvements achieved with Cs have been more modest than those achieved with the (more directly-comparable) broadband sources—in large part due to the difficulty of red-side tuning the Cs VHG-narrowed lasers equivalent to that for Rb. More generally, Cs lasers are simply not as widely available, nor

is SEOP with Cs as widely explored. Furthermore, unlike our consortium's open-source hyperpolarizer,^{44,45} few SEOP devices have been designed with Cs-related upgrades in mind—and thus switching from Rb to Cs would be a time-consuming prospect that would require not only switching out the expensive laser, but most of the other optical components as well.

Correspondingly, we have begun to investigate an approach that, if successful, would allow one to exploit the advantages of Cs for hyperpolarizing ^{129}Xe (or other isotopes) while still using the same instrumentation used for Rb/Xe SEOP: Rb/Cs “hybrid” SEOP.⁸⁹ Hybrid SEOP was first proposed by Happer *et al.*⁸⁴ and demonstrated by Babcock *et al.*⁸⁰ for Rb/K/ ^3He SEOP; those results found that SE efficiencies of a Rb/K hybrid cell exceeded that of pure Rb by an order of magnitude with greater polarizations being observed for K/Rb ratios of 2–6.^{80,85} There, the idea was to exploit the lower spin-destruction rates that K has (*versus* Rb) for ^3He , while exploiting the more favourable lasers (and higher vapour pressure) with Rb. Here, our ongoing work explores an analogous system of Rb/Cs/ ^{129}Xe , in which angular momentum is transferred from optically pumped Rb to ^{129}Xe *via* the auxiliary alkali metal Cs. Theoretically, this pathway may be more favourable than direct Rb– ^{129}Xe OP by possibly providing faster SE rates or higher polarizations; in addition to the higher Cs/Xe SE cross-sections reported above, the SE cross section for Rb–Cs has been reported to be $2.3 \times 10^{-14} \text{ cm}^2$, slightly larger than corresponding values for both Rb–Rb ($1.9 \times 10^{-14} \text{ cm}^2$) and Cs–Cs ($2.2 \times 10^{-14} \text{ cm}^2$).^{16,86}

Although these efforts had just begun at the time of writing this chapter, to date we have been able to achieve high ^{129}Xe polarizations of $P_{\text{Xe}} \approx 50\%$ with a 100 Torr Xe, 1900 Torr N_2 cell, nearly breaking even with equivalent results using pure Rb. The mass ratio of Rb : Cs in this case was 10 : 1, where the vapour pressures of the metals was assumed to be governed by their colligative properties, as modelled by Raoult's Law. Thus, it is possible that future hyperpolarizers may be able to utilise a Rb–Cs hybrid vapour with existing Rb lasers if the full potential gains observed with Cs SEOP can be realised *via* the hybrid pathway. However, the situation is not directly comparable with the Rb/K/ ^3He case; here, the *auxiliary metal* (Cs) is the one with the higher intrinsic vapour pressure. The implications of this fact, along with more detailed studies of hybrid SEOP utilizing simultaneous measurements of $[\text{Cs}]$, $[\text{Rb}]$, P_{Cs} , P_{Rb} , P_{Xe} , T_{cell} , and T_{N_2} , will be the subject of future efforts.

Acknowledgements

We thank the Editors for the invitation to contribute this chapter, and the anonymous reviewer for many suggestions to improve it. It is a pleasure to acknowledge Matt Rosen and Sam Patz, as well as a many other collaborators and co-authors, for their contributions to the efforts presented in this chapter.

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CHAPTER 7

T₁ Relaxation of ¹²⁹Xe and How to Keep it Long

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7.1 Introduction

While one needs to understand the physics of spin-exchange optical pumping (SEOP) to generate hyperpolarized (HP) ¹²⁹Xe in the first place, it is equally important for preserving the hard-won polarization from being lost to thermal relaxation. At long times, the equation for the transient build-up of ¹²⁹Xe nuclear spin polarization P_{Xe} during SEOP approaches

$$P_{\text{Xe}} \rightarrow \langle P_{\text{Rb}} \rangle \frac{\gamma_{\text{se}}}{\gamma_{\text{se}} + \Gamma} \quad (7.1)$$

where Γ is the ¹²⁹Xe longitudinal autorelaxation rate, *i.e.*, the rate due to all other mechanisms besides the spin exchange rate γ_{se} . Typical times are minutes to a few tens of minutes for γ_{se}^{-1} and tens of minutes to hours for Γ^{-1} . Hence, Γ limits the maximum nuclear polarization to some fraction of the time- and volume-averaged Rb polarization $\langle P_{\text{Rb}} \rangle^{\dagger}$ in a SEOP cell. In general, Γ has a significant component arising from extrinsic, potentially

[†]We refer generically to rubidium (most commonly used in SEOP) as the alkali metal in SEOP; others (notably cesium and potassium) are also employed.

manageable sources (most notably collisions with the cell walls); the study and control of the relaxation mechanisms that give rise to Γ is thus crucial to efficient production of HP xenon. Moreover, Γ , which generally depends on temperature, applied field, and wall characteristics (including presence or absence of a coating) defines the useful lifetime of a hyperpolarized sample produced by SEOP. Various polarization/storage schemes also make use of different xenon phases, for which Γ can vary dramatically.

Beyond its direct relevance to high-volume production of HP xenon, the study of nuclear spin relaxation of ^{129}Xe has a long history within the context of NMR. As early as the 1950s it emerged as a model system (in the liquid and solid phases) for study of spin-relaxation phenomena, chemical shielding, and hopping motion of atoms in a lattice. Several advantageous properties made ^{129}Xe one of the early alternatives to protons amenable to intensive study with NMR, including: its significant abundance in natural xenon (26%), simple monatomic nature, spin of 1/2, medium-sized magnetic moment (similar to ^{13}C), modest solid-state line width (about 300 Hz at 77 K), and the ease with which one can move across its phase diagram. Earlier studies naturally focused more on *intrinsic* relaxation phenomena at high xenon densities, where relaxation times are also short enough to be measured with conventional thermally-generated NMR. The emergence of HP xenon in the 1970s and 1980s focused more attention on *extrinsic* phenomena, particularly the thorny problem of relaxation due to collisions with container walls. The successful freezing of HP ^{129}Xe with little to no polarization loss led to studies of extraordinarily long T_1 times in the solid at 120 K and below. These results became particularly relevant with the emergence of “continuous-flow” schemes for producing large amounts of HP ^{129}Xe , which rely on cryogenic separation and storage of the polarized xenon. In recent years, intrinsic mechanisms in the gas phase have been revisited with the discovery of the importance of Xe_2 van der Waals dimers to T_1 .

Our purpose here is thus to categorize and review the relaxation mechanisms for ^{129}Xe , as well as provide, where appropriate, practical guidelines under the various relevant conditions for maximizing T_1 .

7.2 ^{129}Xe T_1 in the Gas, Liquid, and Supercritical Phases

In the non-solid phases, relaxation mechanisms for ^{129}Xe can be usefully categorized by the following equation:

$$\left(\frac{1}{T_1}\right) = \left(\frac{1}{T_1}\right)_{\text{It}} + \left(\frac{1}{T_1}\right)_{\text{Ip}} + \left(\frac{1}{T_1}\right)_{\text{Ew}} + \left(\frac{1}{T_1}\right)_{\text{Eg}} + \left(\frac{1}{T_1}\right)_{\text{Eo}}, \quad (7.2)$$

where upper-case subscripts refer to (I)ntrinsic and (E)xtrinsic mechanisms, and lower-case subscripts respectively refer to (t)ransient Xe_2 dimers, (p)ersistent Xe_2 dimers, (w)all collisions, magnetic-field (g)adients, and

interactions with molecular (o)xygen. This classification scheme is not strictly comprehensive: the last term is one of many terms involving binary collisions of ^{129}Xe with other molecules—the oxygen term is the most relevant for applications such as lung imaging. We will not consider contributions from persistent dimers formed by xenon and other molecules (e.g., nitrogen),^{1,2} which appear to play at most a minor role.

7.2.1 Intrinsic Mechanisms

Early studies by Carr and co-workers³ identified the spin-rotation Hamiltonian

$$\mathcal{H}_{\text{sr}} = c_K(r) \mathbf{N} \cdot \mathbf{K} \quad (7.3)$$

as the mechanism for relaxation, where $\mathbf{K}$ is the ^{129}Xe spin, $\mathbf{N}$ is the orbital angular momentum of the Xe_2 dimer in units of $\hbar$, and $c_K(r)$ is the coupling coefficient (in units of energy) as a function of the atomic separation r . This mechanism was originally formulated by Torrey⁴ and is related to chemical shielding of ^{129}Xe nuclei (see Chapter 2). It is much stronger than the ^{129}Xe – ^{129}Xe (or ^{129}Xe – ^{131}Xe) nuclear dipole–dipole interaction that dominates the intrinsic gas-phase relaxation of ^3He ;⁵ the resulting relaxation rates derived from eqn (7.3) are thus independent of the xenon isotopic fractions. In essence, magnetic fields are generated by moving electrons in the highly polarizable Xe atoms during both binary collisions (transient dimers) and the lifetime of Xe_2 van der Waals molecules (persistent dimers). These fields are modulated by the dimer lifetime, leading to relaxation proportional to the spectral intensity of the fluctuations at the ^{129}Xe Larmor frequency. Remarkably, the interaction given by eqn (7.3) is almost entirely responsible for intrinsic relaxation of ^{129}Xe across all regimes of phase, applied field, and temperature, particularly for those relevant to SEOP and the applications of HP gases. For our purposes, T_1 relaxation in the liquid, supercritical, and gas phases (provided the xenon density $[\text{Xe}] > 50 \text{ amgt}$) well satisfies the original empirical formula of Carr and co-workers:^{3,6}

$$[\text{Xe}]T_1 = 56 \text{ h} \cdot \text{amgt} \quad (7.4)$$

at 25 °C. The linear dependence on $[\text{Xe}]$ is characteristic of binary collisions (transient Xe_2 dimers), corresponding to the first term in eqn (7.2). Eqn (7.4) accurately predicts $T_1 \approx 20 \text{ min}$ for ^{129}Xe in the liquid phase.⁷

Although the low NMR sensitivity of thermally polarized ^{129}Xe and the increasingly long T_1 values precluded data from being acquired for $[\text{Xe}] < 50 \text{ amgt}$, the result given by eqn (7.4) was reasonably extrapolated down to $\approx 1 \text{ amgt}$, a density more relevant to SEOP for which eqn (7.4) predicts $T_1 \approx 56 \text{ h}$, assuming binary collisions only. Thus, as SEOP-based production schemes for HP ^{129}Xe were developed, intrinsic mechanisms were largely ignored, considering that T_1 values due to wall relaxation were known to range from tens of minutes to a few hours (see Section 7.2.2).

In 2002, Chann *et al.*¹ showed that in addition to the density-linear term in eqn (7.4), there is a second term that dominates at total gas densities on the order of 1 amgt due to the formation and break-up of Xe₂ persistent dimers (van der Waals molecules). Although only about 0.5% of the atoms in xenon gas at STP are bound in such molecules,⁸ which form and break-up in three-body collisions, the molecular lifetime $\tau_p \approx 1$ ns is about three orders of magnitude longer than the binary-collision lifetime. We note that in the following description, τ_p is strictly defined as the correlation time for molecular reorientation (including break-up) by a third-body; the notion that the first three-body collision generally tends to break-up the weakly bound molecule (and that τ_p can therefore be thought of as the molecular lifetime) is supported by the associated data.^{1,9} The persistent-dimer rate is given by the product of four factors:⁹

$$\left(\frac{1}{T_1}\right)_{\text{ip}} = (2\mathcal{K}[\text{Xe}])M^{\text{sr}}\left(\frac{\tau_p}{1 + \omega^2\tau_p^2}\right)\left(\frac{1}{1 + r_{\text{B}}[\text{B}] / [\text{Xe}]}\right) \quad (7.5)$$

The first factor is the fraction of xenon atoms bound in molecules, where $\mathcal{K}$ is the chemical equilibrium coefficient and the expression is valid in the limit $[\text{Xe}_2] \ll [\text{Xe}]$. The second factor is the spin-rotation second moment $M^{\text{sr}} = (2/3)\langle c_k^2 N^2 \rangle$, where the bracketed expression is the mean-squared interaction strength. The third factor is the power spectrum for collision-induced field fluctuations, where ω is the ¹²⁹Xe Larmor frequency, and we have assumed that the correlation time τ_p is equal to the molecular lifetime of the weakly bound dimers. The fourth factor accounts for suppression of the molecules by adding a second gas with concentration $[\text{B}]$ that can break up persistent Xe₂ dimers with relative efficiency r_{B} . Measurements of r_{B} for various gases are given in Table 7.1; in general larger molecules, especially diatoms such as N₂, have higher kinetic cross sections and are more effective at breaking up the Xe₂ persistent dimers.

Table 7.1 Measured room-temperature coefficients K_{B} ($\times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$) for the break-up of Xe₂ dimers by various gases, including xenon itself. The relative break-up coefficient in eqn (7.5) is given by $r_{\text{B}} = K_{\text{B}}/K_{\text{Xe}}$.

Gas	K_{B}
Xe	1.2 ^a
	3.7 ^b
N ₂	1.3 ^a
	1.9 ^b
He	0.30 ^a
Ar	0.59 ^a

^aMeasured by Chann *et al.*¹

^bMeasured by Anger *et al.*⁹

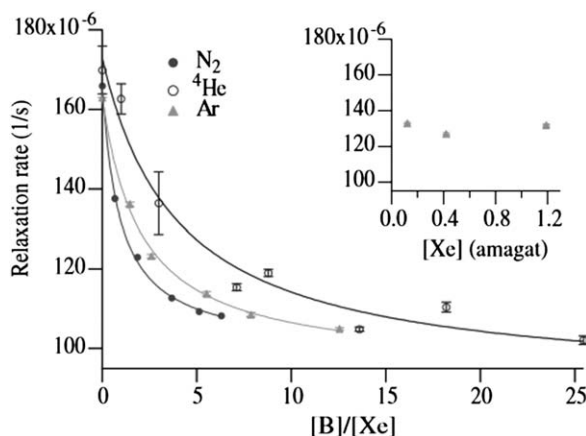


Figure 7.1 Xe spin-relaxation rate as a function of composition for various buffer gases at a fixed Xe partial density of 0.15 amg. The applied field is 24 G, well into the fast-fluctuation limit, $\omega^2\tau^2 \ll 1$ of eqn (7.5). The persistent-dimer rate is suppressed by the addition of a second gas that can break-up Xe₂ dimers. The rate approaches the same pure-xenon rate for all gases as [B] goes to zero and approaches the wall-relaxation rate for the container as [B] $\gg$ [Xe]. Inset: relaxation rate for [Ar]/[Xe] = 1.75 as a function of Xe density; at fixed gas composition, the relaxation is independent of density.

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In the fast-fluctuation limit $\omega^2\tau_p^2 \ll 1$, which holds for applied fields below a few Tesla, the power spectrum reduces to τ_p , which is inversely proportional to the total gas density at fixed composition. From eqn (7.5) we can then conclude that low-field persistent-dimer relaxation is *density-independent* for a fixed gas composition. This key result is seen in Figure 7.1 (inset) from which the authors¹ extract a limiting maximum $T_1 = 4.1$ h for pure xenon at room temperature. Anger *et al.*⁹ performed measurements in applied fields up to 14 T and total gas densities down to ≈ 0.05 amgt (shown in Figure 7.2) that demonstrate the suppression of persistent-dimer relaxation (lower left of Figure 7.2) as the term $\omega^2\tau_p^2$ becomes no longer negligible. They further confirm that for applied fields above a few tesla, the chemical-shift anisotropy (CSA) interaction adds an additional term to the second moment in eqn (7.5) that is proportional to the square of the applied field, a mechanism that was first observed in ¹²⁹Xe by Moudrakovski *et al.*¹⁰ A formula that combines all of these results for intrinsic gas-phase relaxation in the fast-fluctuation limit at 293 K is given by:⁹

$$\left(\frac{1}{T_1}\right)_I = \frac{[\text{Xe}]}{56.1 \text{ h}} + \frac{1}{4.59 \text{ h}} \left[1 + (3.65 \times 10^{-3}) B_0^2\right] \left(1 + r_B \frac{[\text{B}]}{[\text{Xe}]}\right)^{-1}, \quad (7.6)$$

where the gas densities are in amagats, the applied field B_0 is in Tesla, and the low-field pure-xenon relaxation time of 4.59 h measured by Anger *et al.*⁹

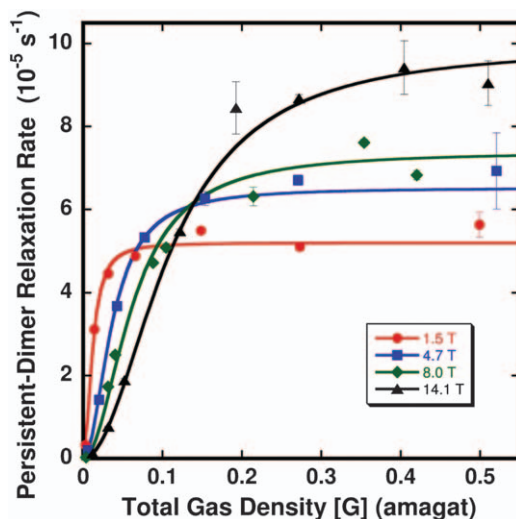


Figure 7.2 Plot of the room-temperature ^{129}Xe persistent-dimer relaxation rate vs. total gas density $[G] = [\text{Xe}] + [\text{N}_2]$, for a fixed relative xenon concentration of 91% at four different values of the applied magnetic field B_0 . The asymptotic rates at large $[G]$ correspond to the limiting minimum rate in the fast-fluctuation limit of eqn (7.5). Above a few Tesla, this asymptotic rate picks up a quadratic dependence on B_0 due to the chemical-shift-anisotropy (CSA) interaction. The rates at small $[G]$ and large B_0 are suppressed as $\omega^2\tau_p^2$ becomes comparable to unity. The lines are fits of the data to a reparameterized version of eqn (7.5) that includes the CSA interaction (the wall relaxation rate was subtracted from these data). Reprinted with permission from Anger *et al.*, *Phys. Rev. A*, 2008, 78, 043406. Copyright 2008 by the American Physical Society.

is 10% longer than that found by Chann *et al.*¹ The linear (transient-dimer) term is expected to depend on temperature as $T^{1/2}$, and this is used to correct slightly the 1-amg relaxation time from the 25 °C data taken by Streever and Carr.⁶ From an analysis⁹ of the temperature dependence of each of the factors in eqn (7.5), there should be little or no overall temperature dependence of the persistent-dimer term, yet Anger *et al.*⁹ found it to be proportional to $1/T^2$ out to ≈ 150 °C. Hence, going to higher temperatures may be an additional avenue (if one cannot add N_2 or other gases to the mixture) to suppressing persistent-dimer relaxation.

7.2.2 Wall Relaxation

There is perhaps no subject generally pertaining to hyperpolarized noble gases that has been more vexing over the past 50 years than the nature of longitudinal relaxation of nuclei to the walls of the (usually glass) containing vessel or cell. The third term in eqn (7.2) is almost always a significant

fraction of the total autorelaxation rate. The highly deformable electron cloud and the ~ 0.1 eV van der Waals surface-binding energy of xenon¹¹ means that wall relaxation times vary widely depending on the size, surface material and/or surface coating, temperature, and applied magnetic field (some who have studied this problem for far too long might also include the phase of the moon!). Indeed, a fundamental problem with any attempt to study wall relaxation is that systematic variation of some important parameters (*e.g.*, gas density, gas mixture, cell size) often requires fabrication of a series of cells with reproducible wall characteristics. Temperature can only cleanly be varied below about 50 °C, as the Rb–¹²⁹Xe spin-exchange rate (*via* [Rb]) is otherwise non-negligible and exponentially sensitive to temperature.[‡] Applied magnetic field and temperature are thus the most common variable parameters that have been studied systematically.

There are other, even more difficult variables, such as the myriad protocols and steps taken to remove impurities from or apply coatings to cell walls prior to introducing Rb and Xe—a specific step or practice may be regarded by one research group as essential and by another as irrelevant, with a paucity of hard reproducible data to resolve the difference. Cell aging or “curing”,¹³ whereby wall characteristics change over hours, days, or even months and years, further confounds a systematic analysis, even within one research group. We will not concern ourselves here with excessively detailed descriptions of various cell-making protocols. Glass is a natural choice for cells, as it is transparent to laser light, chemically resistant, and impermeable to air and water that would react with the alkali metal. Most protocols attempt to clean and purify the glass in some way by heating and evacuation prior to applying the surface coating and then introducing some macroscopic amount of Rb metal. Two examples of detailed protocols for cell making are given by Zeng *et al.*¹⁵ and Breeze *et al.*,¹⁶ where, among other differences, the former prepares cells entirely under vacuum, including distillation (“chasing”) of Rb with a flame, while the latter introduces Rb to the cell in a glove box under an inert atmosphere. Both assert that in small (droplet) quantities, the Rb has minimal effect on the coating. In the presence of higher laser intensities, higher temperatures, and greater amounts of Rb, other groups⁹ have reported some instability in T_1 related to the interaction of Rb with the wall coating.

Despite this rather daunting landscape, we will venture here a few basic guidelines specific to ¹²⁹Xe wall relaxation (³He, much smaller with almost

[‡]Saturated vapor pressure *vs.* temperature curves, such as that due to Killian,¹² are widely cited as surrogate measurements of [Rb]. Care must be taken, however, as high-power diode lasers, increasingly used in SEOP over the last two decades, can significantly increase [Rb] over the value indicated by the temperature of the cell wall or of the air in a surrounding oven. Specific chemistry of Rb metal with the wall or wall coating may also affect [Rb], even in cases of minimal laser power or where the temperature is otherwise known precisely.¹³ Experiments that depend on accurate knowledge of [Rb] should measure it with more precise optical techniques, such as Faraday rotation.¹⁴

no van der Waals interaction, exhibits very different characteristics) with the caveat that there are likely more exceptions than rules:

- Bare (uncoated) glass cells vary widely in relaxation characteristics (less than a minute to more than an hour); a trial-and-error approach making many cells can work but is tedious.
- Cells coated with silane- or siloxane-based materials (*e.g.*, SurfaSil, dichloro-dimethylsilane) are more consistent but not spectacular, with typical low-field T_1 ranging from 20–40 min.
- Cells can age over hours, days, weeks, or more. Heating/SEOP cycles can play a significant role in this process. Generally, a large amount of Rb metal in the cell degrades the coating over time.
- Unlike the counterintuitive case of ^3He , smaller surface-to-volume ratio increases T_1 .
- Owing to the previous bullet points, low-field T_1 can be improved to at least a few hours by using larger regularly-shaped coated cells that contain little to no Rb.
- Increasing the applied magnetic field also increases T_1 , up to several hours or more in fields of several Tesla.

While providing some justification for these guidelines, we will also give an overview of work primarily concerned with ^{129}Xe wall relaxation, although some other important results have emerged in the context of studies with different primary goals.

In almost all cases, wall relaxation operates in the weak-relaxation limit $\alpha \ll \lambda/R$, where α is the relaxation probability per wall collision, λ is the mean free path (≈ 50 nm for STP xenon), and R is the characteristic cell dimension. This assumption leads to:¹⁷

$$\left(\frac{1}{T_1}\right)_{\text{Ew}} = \frac{\alpha \bar{v} S}{4V} \quad (7.7)$$

where $\bar{v}$ is the rms thermal speed of the atoms and S/V is the surface-to-volume ratio of the cell. We note that while S is generally proportional to the macroscopic inner surface area of the cell, it is actually an effective cross-section for a spin to encounter some relaxing perturbation (*e.g.*, a paramagnetic defect or impurity), and may depend on the microscopic surface topography and/or the nature and concentration of relaxing sites on the surface. A spherical cell having radius $R = 1$ cm containing 1 amgt of xenon with $T_1 = 20$ min at room temperature yields an average number of required wall collisions $\alpha^{-1} \approx 2 \times 10^7$ to depolarize a ^{129}Xe atom. A practical way to express this limit is $\tau_D \ll T_1$, where the diffusion time across the cell $\tau_D \approx R^2/D$. Our example above has $\tau_D \approx 20$ s, and we conclude that to violate this limit, most cells would have an impractically large α and short T_1 . Eqn (7.7) implies that the relaxation depends only on the relative flux of atoms to the wall and is thus *independent of gas density*, a finding that has been broadly verified for both ^3He and ^{129}Xe .^{1,5,9,17} The linear dependence on S/V has also

been verified, most recently by Möller *et al.*¹⁸ in experiments with flexible polyvinyl fluoride (Tedlar) bags where T_1 was monitored as a function of the level of inflation. It was also elegantly demonstrated¹⁶ with a series of spherical coated cells of varying S/V .

Another possible kinetic model for wall relaxation¹⁷ is based on the cell having a limited number of relaxive sites on the surface with characteristic residence time τ_r , such that a ^{129}Xe spin would only be perturbed in some small fraction of wall collisions (reducing the effective S). In the limit of low gas density where only a small fraction of such sites are occupied at any time, eqn (7.7) still holds. However, if at higher densities the relaxing sites are mostly occupied, then the wall relaxation rate decreases with density as the site-occupation saturates. The vast majority of studies do not observe relaxation behavior consistent with this model. In a few instances where anomalous behavior inconsistent with eqn (7.7) has been observed, the intrinsic persistent-dimer mechanism discussed above was not accounted for.^{10,16} For a fixed gas composition, persistent-dimer relaxation can be mistaken for wall relaxation because both are density-independent.

Early low-field (1–30 G) studies of ^{129}Xe wall relaxation established siloxane-chain polymer coatings as superior to bare borosilicate (Pyrex) glass.¹⁹ While cell-to-cell variations of 30–50% are still the norm in coated cells, $T_1 \geq 20$ min is almost always observed, whereas bare-glass cells exhibit shorter and even more widely varying T_1 values. These early studies also appear to have established the siliconizing agent SurfaSil (Pierce Scientific)¹⁶ as the most widely used coating; it is typically prepared as a 10% mixture in cyclohexane. Multiple groups^{15,20,21} have also reported that several hours to a few days of heating or “curing” of such cells is required to achieve a Rb density in the neighborhood of the expected value at SEOP temperatures.¹² Several different siloconizing agents and chemical coatings have also been successfully employed, some with 20–30% longer T_1 values than for SurfaSil, whereby we note that these measurements²¹ were made in a much higher magnetic field (4.7 T) with baseline T_1 values of a few hours.

The use of organic-polymer coatings was likely inspired by earlier use of siloxane and paraffin coatings to inhibit the wall relaxation of optically pumped alkali-metal atoms in vapor cells.²⁰ A more systematic and quantitative approach would naturally seek materials with low binding affinity for xenon, assuming an Arrhenius relation for the dwell time τ_d of xenon adsorbed to the surface:

$$\tau_d = \tau_0 e^{-E_a / kT} \quad (7.8)$$

where the binding energy $E_a \sim 0.1$ eV and $\tau_0 \sim 1$ ps is a characteristic vibrational period. As xenon is known to diffuse into many organic polymers, siloxane-polymer-chain coatings that have abundant high- γ protons might not appear to be the best candidates to inhibit wall relaxation. A few other coatings, such as RbH,²² have also been investigated. Yet, until recently (see below), SurfaSil and similar coatings have provided the best and most consistent long- T_1 results. A plausible hypothesis for why these coatings

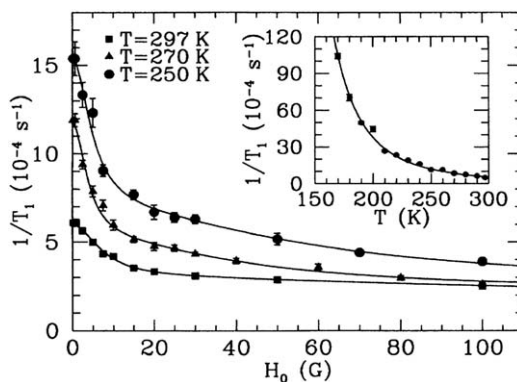


Figure 7.3 Plot of ^{129}Xe T_1 vs. magnetic field for a 1 cm^3 Pyrex cell coated with SurfaSil at three different temperatures. The fits correspond to a model of dipole-dipole relaxation, where the correlation time $\tau_c = 8\text{ }\mu\text{s}$ for relaxation to proton spins. The zero-field temperature dependence (inset) allows a calculation of the site-binding energy, yielding $E_a = -0.10\text{ eV}$ and a dwell time $\tau_d \approx 50\text{ ps}$, according to eqn (7.8). The magnetic decoupling width is a few Gauss and independent of temperature, indicating that that dwell time τ_d at a surface site should be even greater than τ_c , which is clearly not true. The explanation that best fits these observations is that xenon permeates and becomes trapped in the coating for times longer than τ_c . Reprinted with permission from Driehuys *et al.*, *Phys. Rev. Lett.*, 1995, 74, 4943. Copyright 1995 by the American Physical Society.

work is that they cover up much more potent paramagnetic sites on the bare-glass surface, increasing their distance from adsorbed ^{129}Xe atoms. We note here that bulk polymer materials such as polyvinyl fluoride and polytetrafluoroethylene (Teflon) also exhibit relaxation times that are at least comparable to coated cells and are often used (as tubing or bags) to handle, transfer, or store previously polarized HP xenon.^{18,23}

The first comprehensive study of wall relaxation in the presence of coatings, performed by Driehuys *et al.* on SurfaSil,¹¹ unambiguously demonstrated *via* a double-resonance experiment that ^{129}Xe relaxes *via* the dipole-dipole coupling to protons in the coating. The magnetic decoupling curve (Figure 7.3) with a width of just a few Gauss practically demonstrates that one should use applied fields $>10\text{ G}$ with coated cells to avoid rapid relaxation as the ^{129}Xe Zeeman energy begins to approach the proton- ^{129}Xe dipolar coupling. The correlation time associated with relaxation to protons, $\tau_c \approx 8\text{ }\mu\text{s}$, is much longer than any reasonable dwell time τ_d that could be calculated with eqn (7.8). Thus the data suggest that, rather than simple adsorption to the surface, Xe atoms permeate and become trapped in the coating for times even longer than τ_c . The authors further suggest that deuterating the coatings should further suppress relaxation. However, efforts along these lines using deuterated polyethylene and dotriacontane coatings (similar to SurfaSil and comparable in effectiveness) showed no

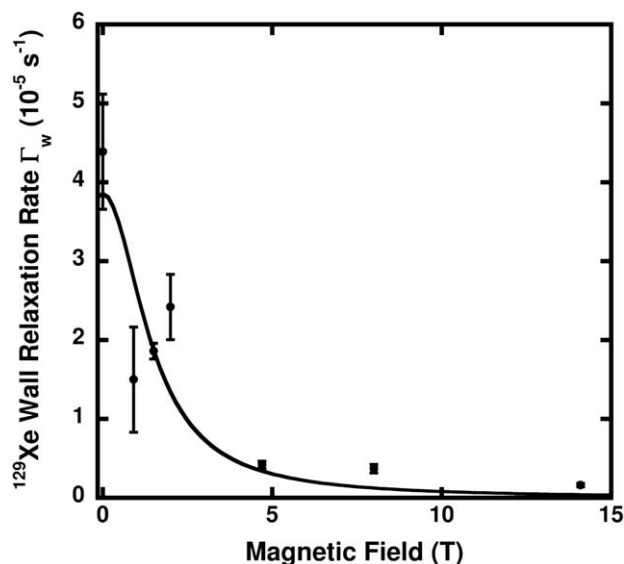


Figure 7.4 Plot of ^{129}Xe wall relaxation rate vs. applied magnetic field for a 6.7 cm-diameter spherical Pyrex cell, Rb-free and coated with SurfaSil. The data show magnetic suppression of the relaxation mechanism with a characteristic decoupling field of a few Tesla. The fit corresponds to a model with the familiar $\tau_c(1 + \omega^2\tau_c^2)^{-1}$ spectral intensity function and yields $\tau_c \approx 4$ ns, consistent with ^{129}Xe interaction with a fluctuating paramagnetic site on or in the wall coating.

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significant or consistent difference in T_1 as compared with the conventional ^1H versions of these coatings.²¹

Starting with the work of Augustine and Zilm,²⁴ several studies^{10,16,21,25} showed that an applied magnetic field B_0 of a few Tesla or more increases the T_1 of coated cells to 3 h or more. Anger *et al.*⁹ still hold the reported record for a measured gas-phase ^{129}Xe T_1 of 99 h at $B_0 = 14.7$ T; this was accomplished in a Rb-free 6.7-cm-diameter spherical Pyrex cell, coated with SurfaSil, containing 12 mbar of xenon (91% ^{129}Xe) and 1.1 mbar N_2 at 295 K. Both the persistent-dimer relaxation (see Section 7.2.1) and wall relaxation were greatly suppressed in this regime. Figure 7.4 shows a plot of wall-relaxation rate vs. magnetic field;⁹ the magnetic decoupling width is a few Tesla, consistent with a correlation time (several nanoseconds) associated with fluctuating paramagnetic sites on the surface or in the coating. Rohrbaugh *et al.*²² find a comparable decoupling field in their study of RbH and RbD coatings.

Longer T_1 's observed in fields of several Tesla or more aren't that practically useful from the perspectives of cost, portability, and commercialization. However, these studies provided valuable insight into the nature of wall relaxation, and with the persistent-dimer mechanism fairly

well understood, progress is now being made to increase gas-phase T_1 at much lower fields. Anger *et al.*⁹ measured $T_1 = 3.4$ h at $B_0 = 30$ G in a Rb-free SurfaSil-coated 12.7 cm-diameter spherical cell containing pure xenon at room temperature, and $T_1 = 5.75$ h in the same cell at $T = 373$ K. Nikolaou *et al.*²⁶ have obtained $T_1 \approx 2$ h at $B_0 = 53$ G in a SurfaSil-coated cell (also containing Rb metal) at $T = 309$ K. Most recently, Heil *et al.*,²⁷ as part of developing a ^3He - ^{129}Xe co-magnetometer for precision fundamental-symmetries measurements, measured $T_1 \approx 11$ h at room temperature in an applied field of only 4 mG. Sufficient nitrogen was added to the gas mixture ($^3\text{He} : ^{129}\text{Xe} : \text{N}_2 \approx 2 : 8 : 35$ mbar) to suppress persistent-dimer relaxation (see Section 7.2.1), so the reported relaxation time is due mostly to wall collisions. The 6 cm-diameter cylindrical glass cell was made of the glass GE-180, cleaned with distilled water and the commercial agent Mucosol. Remarkably no coating or other special treatment of the glass was employed, although only $\approx 25\%$ of the cells made using this protocol exhibit these long T_1 values.²⁸ Aluminosilicate glasses such as GE-180 are widely used for HP ^3He cells, due to their much lower permeability to helium, but almost all other polarization and storage cells for ^{129}Xe are made of standard borosilicate glass (Pyrex or equivalent), whereby it is assumed that it is the coating that largely determines the wall-relaxation characteristics.

Finally, we note that some approaches to the production of HP ^{129}Xe minimize or avoid the issue of gas-phase relaxation altogether: in “continuous-flow” systems (see Chapters 4 and 5) Xe gas is moved so quickly (in tens of seconds to a few minutes) from the cell to a cold trap or directly to an NMR probe, that gas-phase relaxation rates are largely irrelevant. In the case of accumulation at 77 K, frozen xenon is then subject to reliably predictable mechanisms having $T_1 \approx 2.4$ h for $B_0 > 500$ G (see Section 7.3). On the other hand, as wall relaxation times at low field (tens of gauss) and room temperature continue to improve, it may be reasonable to think about employing gas-phase storage at the output of a continuous-flow system, with T_1 significantly longer than 2.4 h and no need for the large magnetic field and cryogens for accumulation. The main disadvantage of this approach is the much greater volume needed to store a given amount of xenon in the gas phase compared to storage as a solid.

7.2.3 Gradient Relaxation

In the context of the early development of the two distinct methods for optically polarizing ^3He gas (SEOP and direct polarization of metastable helium), both Gamblin and Carver²⁹ and Schearer and Walters³⁰ first identified and studied the mechanism of gas-phase relaxation by diffusion through gradients in an applied magnetic field, the fourth term in eqn (7.2). The essential idea is that rapidly moving and colliding gas atoms can easily violate the adiabatic condition that allows spins to follow the field direction for sufficiently gradual changes: $(1/B_0)(dB_{\perp}/dt) \ll \gamma B_0$, where $B_{\perp}$ is the transverse component of an applied field B_0 that is nominally oriented along

Table 7.2 Binary diffusion coefficients $D_{\text{Xe}-i}$ for xenon near room temperature and 1 bar pressure in various gases relevant to the production and applications of hyperpolarized ^{129}Xe .

Gas i	$D_{\text{Xe}-i}/\text{cm}^2 \text{ s}^{-1}$	Ref.
Xe	0.056–0.058	45, 46 and 47
N ₂	0.12–0.13	48 and 49
He	0.56	46 and 47
O ₂	0.14	50

the z (quantization) axis. The result is relaxation that depends linearly on the diffusion coefficient D and quadratically on the relative transverse gradient strength:^{29,30}

$$\left(\frac{1}{T_1}\right)_{\text{Eg}} = D \frac{|\nabla B_x|^2 + |\nabla B_y|^2}{B_0^2}, \quad (7.9)$$

where the usual magnetic-decoupling factor proportional to $(1 + \omega^2 \tau_c^2)^{-1}$ has been omitted,³¹ because $\omega^2 \tau_c^2 \ll 1$ for $B_0 < 20$ T, where τ_c is the diffusion correlation time (*i.e.*, the time between collisions). We note that the zero-curl condition for $\mathbf{B}$ (in regions of no current) assures that the various gradients in any reasonable field geometry (*e.g.*, the Helmholtz arrangement) are the same order of magnitude in any region of space. Gradient relaxation can thus often be estimated by moving a sample along the longitudinal field by some distance and observing the change in Larmor frequency. Binary diffusion coefficients $D_{\text{Xe}-i}$ for xenon in various relevant gases have been measured and are tabulated in Table 7.2, whereby we recall that for the i th gas in a given mixture through which xenon diffuses (in the ideal non-interacting limit), $D_{\text{Xe}-i} \propto T^{3/2}/n_i$ where n_i is the partial gas density. The diffusion coefficient D in eqn (7.9) is thus given for xenon by $1/D_{\text{Xe}} = \sum_i (1/D_{\text{Xe}-i})$.

Cates *et al.*³¹ point out that eqn (7.9) is only valid in the high-pressure limit $\omega R^2/D \gg 1$, where the Larmor period is much shorter than the diffusion time across a cell having characteristic linear dimension R ; they go on to derive expressions for the more general case. However, in almost all situations where HP ^{129}Xe is being made or used, eqn (7.9) is valid; *e.g.*, a spherical cell of radius 0.5 cm containing 0.01 amgt of xenon in a field of 1 G has $\omega R^2/D \approx 370$ and well satisfies the high-pressure limit. A notable exception is more recent fundamental-symmetries work involving ^{129}Xe magnetometry at fields ≤ 0.1 G,^{27,32} for which eqn (7.9) may not always be valid.

7.2.4 Relaxation Due to Oxygen

Molecular oxygen has a permanent electronic magnetic dipole moment (maximum projection on a quantization axis) very nearly equal to two Bohr magnetons. As such, it is a potent agent for ^{129}Xe relaxation, whether present

residually, accidentally, or unavoidably—as with *in vivo* lung MRI. Jameson and co-workers³³ conducted a comprehensive study of collisional dipolar coupling of O_2 with ^{129}Xe in the gas phase. The essential result is:

$$\left(\frac{1}{T_1}\right)_{\text{Eo}} = C(T)[\text{O}_2]F(V/kT), \quad (7.10)$$

where F is a dimensionless functional accounting for deviation from the hard-sphere-collision limit for a given reduced intermolecular potential V/kT , and $C(T)$ is given by:

$$C(T) = \frac{16}{3}S(S+1)\gamma_I^2\gamma_S^2\frac{\hbar^2}{d^2}\left(\frac{\pi\mu}{kT}\right)^{1/2}, \quad (7.11)$$

where $S = 1$ is the O_2 electronic spin, γ_I and γ_S are the gyromagnetic ratios for ^{129}Xe and O_2 , respectively, $d = 3.69 \text{ \AA}$ is the characteristic distance of closest approach, and $\mu = 25.6 \text{ amu}$ is the reduced mass of the $^{129}\text{Xe}-\text{O}_2$ pair. At $T = 300 \text{ K}$, $F(V/kT) = 6.00$ and decreases weakly with increasing temperature. Using the density of an ideal gas at STP, we can write a practically useful formula:

$$\left(\frac{1}{T_1}\right)_{\text{Eo}} = (0.478 \text{ s}^{-1} \text{ amgat}^{-1})n_{\text{O}_2}, \quad (7.12)$$

where n_{O_2} is the oxygen density in amagats, in good agreement with earlier measurements.³ Eqn (7.12) is strictly valid in the low-field limit at $T = 300 \text{ K}$. Apart from the weak temperature dependence of $F(V/kT)$, the rate varies as $T^{-1/2}$ according to eqn (7.11). There is also a weak field dependence $\sim B_0^{1/2}$ due to the form of the spectral density function in the short-correlation-time limit: the rate is reduced by about 10% at 1 T. From eqn (7.12) we see that room air ($\approx 20\% \text{ O}_2$) yields $T_1 \approx 10 \text{ s}$ due to oxygen, an important limitation for applications such as *in vivo* lung MRI.

7.3 ^{129}Xe Relaxation in the Solid Phase

Starting with the work of Driehuys *et al.*,³⁴ understanding T_1 in solid xenon has been of practical importance with the vigorous development of high-throughput continuous-flow ^{129}Xe polarizers (see Chapter 5). The use of a lean-xenon mixture requires that the xenon be separated and then stored as it is being accumulated. A cold trap at $T = 77 \text{ K}$ in a field $B_0 > 1 \text{ kG}$ provides compact storage with $T_1 \approx 2.4 \text{ h}$. We briefly review the mechanisms responsible for this relaxation, particularly in the context of storage and accumulation for continuous-flow systems.

The early work of Cates *et al.*³⁵ in sealed cells demonstrated that the ^{129}Xe hyperpolarization generated by SEOP can survive the phase transition to the solid. A systematic study as a function of temperature T and applied field B_0 was then conducted by Gatzke *et al.*³⁶ The basic features of solid relaxation from that work are that T_1 is broadly field-independent above a few hundred

gauss and for $T=20\text{--}77\text{ K}$; in this temperature regime, T_1 varies approximately as $1/T^2$, with the measured value $T_1 \approx 2.4\text{ h}$ at 77 K . These findings are consistent with relaxation caused by Raman scattering of harmonic phonons; essentially the same spin-rotation interaction introduced in Section 7.2.1 is here modulated by lattice vibrations instead of gas-phase collisions.^{37,38} The temperature dependence is that of the Debye phonon spectrum, modified by a function that accounts for the sharp decrease in phonons below the Debye temperature, where T_1 becomes extraordinarily long (several days or more at 4.2 K).

Gatzke *et al.*³⁶ also observed a significant monotonic decrease of T_1 with decreasing applied field for $B_0 < 500\text{ G}$ at all temperatures; this is due to another mechanism, the nuclear dipole–dipole interaction modulated by vacancy hopping in the lattice.³⁹ Kuzma *et al.*⁴⁰ added a detailed study of the temperature range $120\text{--}160\text{ K}$ and the applied field range $0.067\text{--}1.4\text{ T}$, where vacancy hopping begins to dominate the Raman-phonon process, particularly at low field. They provide a detailed model based on known hopping rates in solid xenon³⁹ that also accounts for various compositions of the non-zero-spin xenon isotopes. For example, in naturally abundant xenon at $B_0 = 0.2\text{ T}$, T_1 drops from $\approx 1\text{ h}$ to $\approx 1\text{ min}$ as the temperature rises from 120 K to 160 K .⁴⁰ These results are of practical importance in continuous flow polarizers, because in a simple and widely used cryogenic trap, the polycrystalline xenon collects in a pile at the bottom of a glass tube immersed in LN_2 . This pile may not have sufficient thermal conductivity with the wall to be entirely cooled to the wall temperature before vacancy hopping rapidly destroys a significant amount of the collected magnetization; see Figure 7.5. Ruset *et al.*⁴¹ addressed this issue by collecting the entire sample in a large thin film on the wall of the cold trap (see Chapter 5).

We note here that insofar as T_1 in solid xenon is dominated by the Raman-phonon scattering mechanism, the relaxation is independent of the xenon isotopic composition. As the phonons are frozen out below the Debye temperature, a residual weak field-dependence to the relaxation is observed.³⁶ In this regime, T_1 is measured in days, but an observed dependence of T_1 on the isotopic fraction of ^{131}Xe supports the hypothesis of cross relaxation of ^{129}Xe nuclei with extreme-quadrupolar-broadened ^{131}Xe nuclei at lattice defects and near crystallite surfaces,³⁶ whereupon the magnetization is leaked to the lattice *via* a much faster ($\approx 5\text{ min}$) T_1 for ^{131}Xe .³⁸ In the regime of lower fields, where the vacancy-diffusion mechanism is significant, there is also some mild dependence on isotopic composition,⁴⁰ due to the fact that different compositions create different local-field distributions around the ^{129}Xe .

Overall, the Raman-phonon theory, coupled with vacancy diffusion at higher temperatures, is in reasonably good agreement with most of the data, despite having no free parameters; see Figure 7.6. There is significant scatter in the data—for example, measurements at 77 K range from 120 min to 160 min . Recent work by Limes *et al.*⁴² (to be published) achieved unprecedented precision and reproducibility in T_1 measurements at $T = 77\text{ K}$

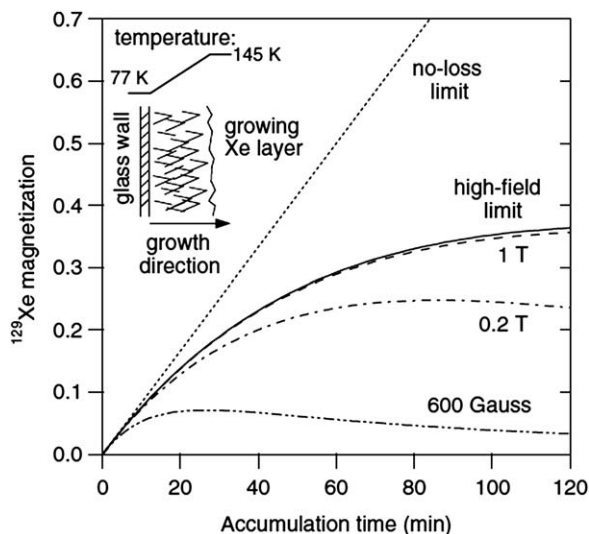


Figure 7.5 A simulation of performance for a simple liquid nitrogen cryo-trap accumulator, assuming a linear temperature profile (77–145 K) across the accumulating pile of Xe snow. After 15 min of accumulation at 0.06 T (lowest curve), the magnetization is about 50% of the no-loss limit. The model demonstrates the importance of maintaining the entire accumulated sample at 77 K. Reprinted with permission from Kuzma *et al.*, Phys. Rev. Lett, 2002, **88**, 147602. Copyright 2002 by the American Physical Society.

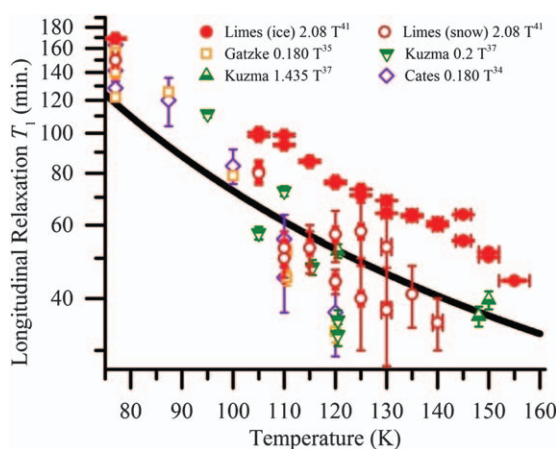


Figure 7.6 A summary of reported T_1 measurements of ^{129}Xe in solid xenon with references given. Measurements are on snow except for ice data from Limes *et al.*⁴² (solid red circles) and data from Kuzma *et al.*⁴⁰ The ice data of Limes *et al.*⁴² show measured T_1 's 40–50% longer than predicted by the Raman-phonon scattering theory³⁷ (black line). Copyright 2014 by M. E. Limes and B. Saam.

and from $T = 105\text{--}155\text{ K}$ in a field $B_0 = 2.0\text{ T}$. In this regime, Raman-phonon scattering³⁷ is the only significant relaxation mechanism, and it should not depend on the specific size or orientation distribution of the crystallites in the polycrystalline sample. Limes *et al.*⁴² found significant and reproducible differences in T_1 for samples condensed directly from xenon gas as white “snow” vs. samples which are sufficiently warmed to become entirely liquid and then refrozen as a single plug of translucent “ice.” For ice they measured $T_1 = 169.2 \pm 1.2\text{ min}$ at 77 K as a weighted average of ten separate measurements. A similar data set for snow yielded $T_1 = 149.9 \pm 0.5\text{ min}$ at 77 K , which is more in line with previous measurements, most of which were on snow samples (the ice measurements of Kuzma *et al.*⁴⁰ are an exception[§]). The data produced by Limes *et al.*⁴² show T_1 values longer than any previous measurement and 40–50% longer than the Raman-phonon theory³⁷ across all temperatures measured (Figure 7.6); these results may indicate the need to reconsider the completeness of the Raman-phonon theory and/or its fixed input parameters.⁴³

An additional finding of Limes *et al.*⁴² may at least partially explain the snow–ice discrepancy: the large surface-to-volume ratio of snow samples allows significant relaxation from surface-adsorbed paramagnetic molecular oxygen, which may exist in residual or outgassed concentrations in cold traps where ^{129}Xe accumulation is taking place. In low concentrations, O_2 would add a small rate to the Raman-phonon rate by relaxing ^{129}Xe atoms located at or near crystallite surfaces. At higher O_2 concentrations, where the surface polarization is kept near zero, the effect of O_2 would eventually be limited by ^{129}Xe spin diffusion to the surface. The effects of O_2 have been demonstrated by intentionally admitting air to a sample chamber containing snow prior to starting a T_1 measurement at 77 K . Two such measurements are shown in Figure 7.7. In both cases, the relaxation in the first $\approx 100\text{ min}$ was measurably faster than the late-time monoexponential rate. In one case, after the late-time regime had been reached, the sample was exposed to air for a second time with no measurable effect on the signal decay; apparently, the first exposure to O_2 depolarized all of the ^{129}Xe atoms at or near a crystallite surfaces. Spin diffusion in xenon into the bulk is slow enough ($7 \times 10^{-14}\text{ cm}^2\text{ s}^{-1}$ for ^{129}Xe in naturally abundant xenon⁴⁴) that for reasonably sized crystallites it would constitute only a small contribution to the total relaxation rate. However, it is striking that the late-time rates seen in Figure 7.7 correspond to the longest T_1 ’s measured by Limes *et al.* in snow samples. Similar oxygen experiments were done on ice samples with no effect on the decay rate.

[§]Kuzma *et al.*⁴⁰ warmed their samples to 190 K to liquefy the xenon before cooling down to solid temperatures in an effort to collect all of the solid that had deposited on the walls of their cold trap; they tried to perform these steps quickly, so as to avoid a severe loss of polarization. In performing a similar sequence of steps to liquefy a snow sample, Limes *et al.*⁴² verified by monitoring the NMR spectrum that each of their samples was entirely liquid prior to re-freezing.

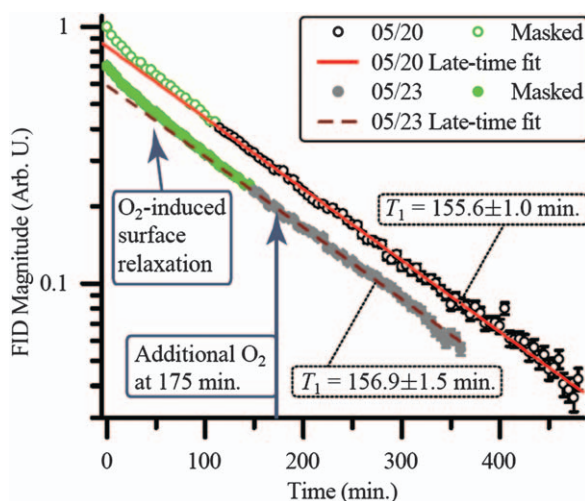


Figure 7.7 Plots of NMR signal intensity vs. time for two snow samples (identified by date the data were taken). Each sample was exposed to air just prior to the measurement, resulting in the slightly faster rate observed for the first ≈ 100 min. Adsorbed oxygen relaxes ^{129}Xe nuclei at or near the crystallite surfaces only. The data points in this early-time region were masked for the respective fits, and T_1 was determined from the late-time data only. The 05/23 sample was exposed to air a second time with no effect on the decay rate, indicating that the surface ^{129}Xe were completely depolarized by the first exposure to O_2 . Similar experiments to deliberately expose ice samples had no effect on the decay rate.
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Finally, we note that the preparation of an ice sample means that it must pass through conditions of more rapid relaxation, both as the solid approaches the melting point (due to vacancy diffusion) and while it is in the liquid phase ($T_1 \approx 20$ min). Hence, while xenon ice may have longer T_1 than snow, the polarization loss in preparing the ice may not make it practical for accumulation in continuous-flow polarizers.

Acknowledgements

The author gratefully acknowledges M. S. Conradi and B. Driehuys for initial reviews of this chapter and helpful input. He also acknowledges N. N. Kuzma and T. G. Walker for providing original high-resolution figures from their respective publications.

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Hyperpolarized ^{129}Xe NMR in Materials Sciences: Pore Structure, Interconnectivity and Functionality

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8.1 Introduction

Structures, interconnectivity and functionality of micro- and mesopores play an important role in the performance of porous materials. The extent of interconnectivity between nano- or meso- pore domains, the size and geometry of the pores as well as the functionality of the pore surfaces greatly affect many properties of the porous materials. These include molecular accessibility and selectivity, separation and reaction kinetics in catalysis; ion transport and diffusion for energy storage in batteries and super-capacitors; adsorption capacity and kinetics of release in hydrogen storage materials; proton and oxygen diffusion across fuel cell membranes, and *etc.* The pore geometry in most porous materials, even in ordered mesoporous silica, is complex and characterized by interconnected cages, channels and micropores.¹ As a result of these complex topographies, characterization of interconnectivity of the pores in micro- or mesoporous materials is often challenging and mandates for several methods. The most common

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

techniques such as small angle X-ray or neutron scattering, and gas absorption, however, do not provide direct information on how channels and cages are connected.

Over the years ^{129}Xe NMR has been developed into a powerful and robust method for studying porous solids.² The large chemical shift range of ^{129}Xe is strongly dependent on both local environmental and chemical factors such as the composition and functionality of the matrix, nature and concentration of coadsorbed molecules, and the shape and size of resident void spaces.^{2–7} The use of optical pumping approaches for the production of hyperpolarized (HP) xenon⁷ allows for a dramatic increase in the sensitivity of ^{129}Xe NMR up to a factor of 10^4 , enabling these pore characterization studies. Using HP xenon produced under continuous flow (CF) conditions, measurements are possible at very low concentrations of xenon, which minimizes the contribution from Xe–Xe interactions to the observed chemical shift. As such, the observed ^{129}Xe chemical shifts can be assigned principally to the interactions between xenon atoms and porous surfaces. Since spin polarized Xe gas percolates through the interconnected pores and samples the local pore environments, HP ^{129}Xe NMR has the unique advantage of directly probing not only these buried interfaces but also the interconnectivity between the pores.

^{129}Xe NMR has been applied to the studies of crystalline porous materials such as zeolites extensively.^{4,8,9} The number of ^{129}Xe NMR studies of mesoporous materials has increased recently due to their unique materials properties.^{10–56} Porous materials can be grouped into three classes based on the pore diameters (d): microporous, $d < 2.0$ nm; mesoporous, $2.0 \leq d \leq 50$ nm; and macroporous, $d > 50$ nm. Zeolites are crystalline microporous materials. As compared with zeolites, mesoporous materials are mostly amorphous in nature and have ordered channels with larger pore sizes varying from 2 to 50 nanometres, which give rise to greatly improved ion diffusion and transport properties. Combined with an extremely high internal surface area this makes them very attractive materials in such areas as the catalysis of processes involving transformation of large organic molecules^{57,58} and gives them potential as advanced separation and chromatographic materials.⁵ Chemical applications of these mesoporous materials usually require functionalization of the relatively inactive surface of the internal walls. A broad variety of active organic or inorganic centers can be created in the channels of the materials, opening up numerous applications in chemistry and biology.⁵⁹ Several approaches can be used to incorporate organic functional groups and molecules into mesoporous materials, mostly for catalytic applications.⁵⁸ One method for generating functional centers in mesoporous materials is through the post-synthesis attachment of desired molecular species to the walls of the mesoporous channels. This approach has led to the development of a class of hybrid nanoscale materials that has already demonstrated great potential for many applications, such as adsorption, ion exchange, catalysis, and sensing.^{60–64} The assembly of molecular structures in mesopores provides a unique

opportunity for rational engineering of surface properties. Hybrid mesoporous materials with functional molecules show exceptional selectivity and capacity in the adsorption of heavy metal ions from contaminated waste streams.^{60,61} Besides heavy metals, more efficient materials have also been developed for extracting anions like chromate and arsenate⁶² and radionuclides.⁶⁴

In this chapter, we focus on reviewing previous work on probing structures, interconnectivity and functionality for mesoporous materials by using hyperpolarized (HP) ^{129}Xe NMR. Previous studies on microporous materials including zeolites will not be discussed here since they have been reviewed extensively in the past.^{4,8,9} We emphasize several important classes of mesoporous materials including: (a) functionalized ordered mesoporous materials; (b) polymer aerogels; (c) hierarchically ordered mesoporous materials; (d) infiltrated and doped mesoporous materials; and (e) porous electrode materials. Reviews on other important materials such as biomaterials, nanotubes, metal-organic frameworks and one-dimensional channeled materials are given in different chapters. For each class of the materials in the review, examples are given to illustrate how the information on structures, functionality and interconnectivity of the pores is obtained from the HP ^{129}Xe NMR measurements and how the structures, functionality and interconnectivity of the pores influence the materials properties.

The following Sections, 8.1.1–8.1.4, emphasize the background and methodology of HP ^{129}Xe NMR that are relevant to the studies of the mesoporous materials under review.

8.1.1 ^{129}Xe NMR Chemical Shifts

^{129}Xe NMR chemical shifts are sensitive to the local environment of the Xe atom. The observed ^{129}Xe NMR signals for adsorbed xenon are the weighted averages among various environments sampled by a xenon atom within its characteristic diffusion distance, *i.e.* $\delta_{\text{obs}} = \sum_{i=1..n} p_i \times \delta_i$, where δ_i is the chemical shift of xenon adsorbed on site i , p_i is the fraction of xenon atoms in site i , and n represents the total number of sites. In porous silica without paramagnetic impurities and strong adsorption centers, the chemical shift in a site δ_i is a sum of three main contributions:^{65–68} $\delta_i = \delta_0 + \delta_s + \delta_{\text{Xe-Xe}}$. In this formula, δ_0 is the reference shift, which is usually set to 0 ppm, the chemical shift of xenon gas at zero pressure. The term δ_s is the contribution due to the interaction of Xe with the surface. In general, δ_s is characteristic of a given adsorption site and reflects both the chemical composition of the surface and also the geometry of the xenon environment in that particular site. The chemical shift of adsorbed xenon is known to correlate with the characteristic size of the pore space, and several empirical correlations between the chemical shift and the pore size have been proposed.^{5,66,67,69} These correlations are different for different classes of porous materials and there is no single equation that would fit any arbitrary porous material. The correlations were tested most comprehensively for zeolites and

alumino-phosphate molecular sieves^{5,66} (which have voids with a characteristic size between 4–12 Å) and for porous silica and silica gels of different preparations^{70,71} (pores between 20–400 Å). Although the correlations are not general and not very accurate, they can be used to estimate void sizes in systems of a similar nature. Although we discuss only isotropic shifts here, many of the molecular sieves also show Xe chemical shift anisotropy.⁶

The contribution $\delta_{\text{Xe-Xe}}$ arises from Xe–Xe interactions and is dependent on xenon concentration, shifting signals to lower field with higher loading. At very low loading, the contribution from the Xe–Xe interactions is rather insignificant. Only for the highly loaded samples and in continuous flow experiments at very low temperatures, where condensation of xenon is possible, does the effect become appreciable. For xenon pressures of several bars, the $\delta_{\text{Xe-Xe}}$ contribution can be of the order of a few ppm. Similar downfield shifts of the signals due to increased Xe–Xe interactions in the adsorbed layer at low temperature was previously observed on amorphous silica, alumina and silica–alumina.⁷²

An additional factor that can contribute significantly to the observed ^{129}Xe NMR spectra of porous materials, particularly for samples of poorly defined morphology, is the very small size of the particles, which results in an increased exchange between the intra- and extra- particle xenon. The small size of the particles together with the variation in the bulk density arising from differences of powder packing can lead to a variation in line positions, widths and shapes, mostly causing broadening and up-field shifts of the signals. A detailed discussion of the effect of bulk properties on ^{129}Xe NMR of porous materials has been reported previously.⁷³

8.1.2 HP ^{129}Xe NMR Measurements

HP ^{129}Xe NMR measurements for mesoporous materials were taken mostly using homebuilt polarizers which involve a small pumping cell with a larger than 1 atm pressure inside the cell.^{1,36} Recently, a unique polarizer made of a large vertical pumping cell with a pressure smaller than 1 atm was developed by Hersman's group,⁷⁴ producing a large quantity of polarized ^{129}Xe gas for medical imaging. Based on the Hersman design, modified polarizers have been built, making them more affordable for the materials science research.^{10,12,75} Unlike the other HP xenon polarizers, this type of polarizer has a low-pressure environment that avoids quenching the efficient transfer of spin from Rb electron manifold to the Xe nucleus. Efficient use of the pump diode laser power at 795 nm is affected by means of a long path-length cell (1 m), by high Rb vapor density, and by counter flowing the spin exchanged optically pumped (SEOP) gas in a direction opposite to that of laser propagation. The unique arrangement achieves a remarkably high polarization rate (>35%), even at high flow velocity.

There are two types of ^{129}Xe NMR experiments: (i) with samples sealed in glass tubes with a known amount of preadsorbed xenon (NMR using thermally polarized ^{129}Xe); and (ii) with samples in a continuous flow of

hyperpolarized ^{129}Xe . The continuous flow (CF) system for production of the HP xenon has been described elsewhere.⁷⁶ A xenon–helium–nitrogen mixture with a volume composition such as 1%–98%–1% was used in most CF HP experiments. The flow rate was monitored with a Vacuum General flow controller and kept constant in the range of 200–250 scc min⁻¹ (scc min⁻¹ – gas flow normalized to standard conditions) in a typical experiment. In CF HP experiments a flow of HP xenon was delivered directly into the coil region of a modified NMR probe. Temperature dependent chemical shift measurements in the 120–400 K range were performed with a variable temperature probe. The ^{129}Xe NMR chemical shifts were often referenced to xenon gas extrapolated to zero pressure.

Most ^{129}Xe NMR measurements were carried out using a static NMR probe, where a single-pulse (SP) Bloch-decay method was used. However, for some systems, a magic angle spinning probe was used in order to remove the chemical shift anisotropy. A specially designed MAS probe is required for the MAS experiment under a continuous flow (CF) of HP xenon.

8.1.3 2D Chemical Shift Exchange – Pore Interconnectivity

2D ^{129}Xe NMR chemical shift exchange spectroscopy (EXSY) has been used to resolve the origin of the signals in the spectra of adsorbed xenon and to evaluate interconnectivity between different adsorption regions in porous materials. Information on the presence of exchange, the probable exchange pathway and the timescale of the process can be obtained from the 2D-EXSY spectra taken using standard sequences described elsewhere.^{77–82} The intensities of the cross-peaks are proportional to the exchange time (τ) set in the experimental pulse sequence. For the sites without exchange, or when the exchange time τ is set to zero, only intensity on the main diagonal will appear in the spectrum. Standard 2D EXSY is a quantitative experiment, allowing estimation of all of the exchange rates. In most cases, however, quantification is not feasible because of non-equilibrium polarizations, and the fact that lines are not well resolved. In the past, ^{129}Xe 2D EXSY NMR experiments with thermally polarized xenon were used extensively for evaluation of the exchange between various adsorption sites for Xe in zeolites and other materials.^{77–82} The main practical drawback of the technique is that it requires rather long acquisition times. This problem can often be reduced by the use of hyperpolarized xenon. HP Xe is particularly effective in this regard for materials with relatively unrestricted diffusion of xenon and rather long ^{129}Xe relaxation times, which is the case for mesoporous materials including RF aerogels.^{15,16}

8.1.4 Variable Temperature ^{129}Xe NMR – Pore Size and Heat Adsorption

Variations in ^{129}Xe NMR spectra with temperature are sensitive to the dynamics of adsorbed xenon and subsequently to the morphology of

pore space.^{70,72,73,83,84} For a given temperature, the chemical shift is the dynamic average between various xenon environments. By performing variable temperature (VT) ^{129}Xe NMR, it should be possible to differentiate xenon in the micropore and mesopore regions and obtain heats of adsorption. The use of HP Xe removed the limitation of long acquisition times required for thermally polarized Xe because of its low sensitivity and long relaxation times.

The VT dependencies of the chemical shifts in CF HP ^{129}Xe NMR experiments were used to obtain several important parameters including pore sizes and heat of adsorption assuming only a weak adsorption of xenon that can be described by Henry's law.⁷⁰ In the fast exchange approximation the temperature dependence of the observed chemical shift δ for cylindrical pores can be expressed as⁷⁰

$$\delta_{\text{obs}} = \delta_s \left(1 + \frac{B}{Te^{-\frac{\Delta H_{\text{ads}}}{RT}}} \right); B = \left(\frac{V_g}{S} \right) K_0^{-1} \quad (8.1)$$

where V_g is the free volume of the porous materials, T is the temperature, S is a specific surface area, K_0 is the pre-exponential term of Henry's constant, R is the universal gas constant, ΔH_{ads} is the heat of adsorption and δ_s is the component of the observed ^{129}Xe chemical shift characteristic of the interaction between xenon and the surface. Coverage of the surface with xenon in the CF experiments often does not exceed 1 mmol g^{-1} even for the lowest temperatures, which represents a surface coverage of about $100 \text{ m}^2 \text{ g}^{-1}$. Under such conditions δ_s can be approximated by the observed chemical shift of xenon at the lowest observed temperatures before xenon starts to condense ($\sim 180 \text{ K}$ in CF experiments). Parameters such as ΔH_{ads} , and δ_s can be obtained by fitting the experimental temperature dependent chemical shift data using eqn (8.1) of the VT dependencies of the chemical shift. The applicability and limitations of eqn (8.1) for analysis of the temperature dependence of the ^{129}Xe chemical shift have been discussed previously.^{3,70,83} Although eqn (8.1) contains three variables, in reality only two parameters, ΔH and V_g/S , have a pronounced variation and effect on the fit. The situation is further simplified as the possible range of δ_s is well defined from the low temperature measurements. Thus a strongly constrained δ_s effectively reduces the situation to a two-parameter fit. In addition, the ranges over, which the other variables in eqn (8.1) can change, are in fact also well constrained. The preliminary estimates for ΔH have been obtained from adsorption measurements, while the limits on the V_g/S ratio are imposed by the other data such as TEM data.¹³ Considering the rather broad temperature range studied, the results of the fit are sufficiently reliable.

Using empirical chemical shift-pore size correlations (eqn (9) from ref. 70) developed to fit inorganic systems such as MCMs and zeolites,^{3,70} pore size or diameters for mesoporous materials can be estimated using a geometrical model. The results derived in the context of spherical and cylindrical models are to be treated as approximations. The pore sizes should be regarded with

caution, as there may be an unaccounted scaling factor due to the differences in the chemical composition. However, the result of the comparison of two types of pores is sufficiently reliable. For a given model, the resonance with a larger chemical shift often corresponds to a smaller pore size. Since the interparticle spacing is representative of more spherical pores than cylindrical pores, it is reasonable to use the spherical pore model to estimate the pore sizes for all pores formed from the aggregation of the nanoparticles. However, the cylindrical pore model is best suited for the cylindrical mesoporous channels.

8.2 Application of HP ^{129}Xe NMR in Materials Sciences

8.2.1 Functionalized Ordered Mesoporous Materials

Ordered nano- or mesoporosities provide a unique environment for assembling functional nanoscale materials as illustrated in Figure 8.1.

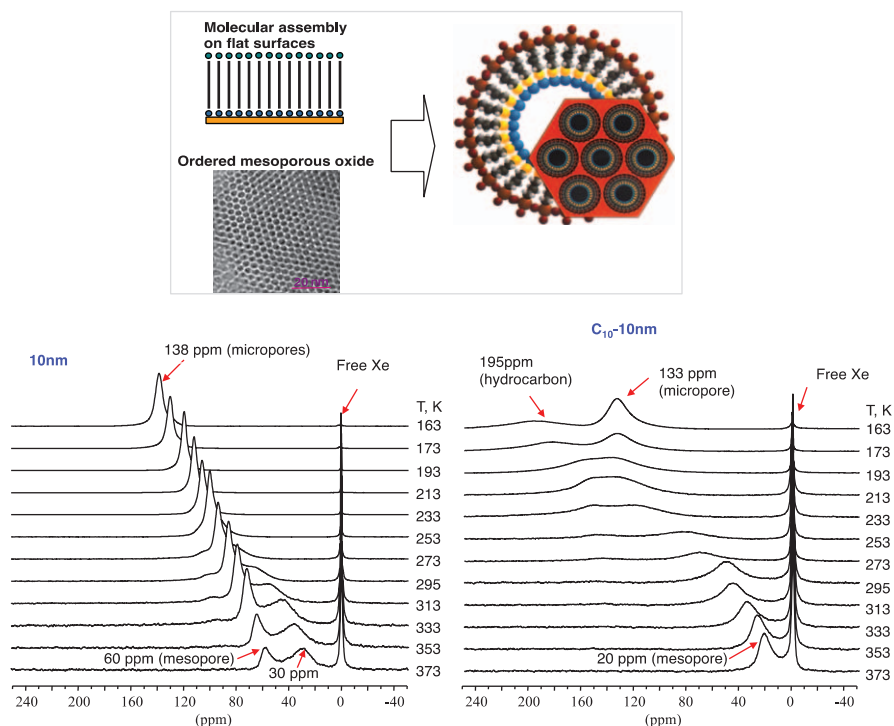


Figure 8.1 Schematic drawing illustrating that ordered nano or mesoporosities (10 nm in diameter) provide a unique environment for assembling functional nanoscale materials (top). Variable temperature CF HP ^{129}Xe NMR for bare mesoporous silica (left) and ordered mesoporous silica (right) functionalized with alkyl silanes (decyltriethoxysilane, referred as C₁₀).

HP ^{129}Xe NMR has been proved to be a powerful tool in probing changes in porosity upon surface functionalization of ordered mesoporous materials.^{23,28–30,37,39} For example, a previous study of ordered mesoporous silica with different porosities and surface functionalization has demonstrated that ^{129}Xe NMR spectra reveal non-uniform porosity and irregular pore structure although N_2 adsorption and TEM show well-ordered nanoporous channels.¹

Spectra in Figure 8.1 showing several overlapping signals for the 10 nm bare silica reveal non-uniform pore environments, although TEM and BET show well-ordered nanoporous channels. Whereas more uniform pore environments are observed for Xe in C_{10} -10 nm, indicating that surface functionalization with organics effectively removes the defects. For 3 nm and 30 nm pore size samples, variable temperature CF-HP ^{129}Xe NMR data (see ref. 1) also reveal distinct adsorption regions. Xe is in fast exchange between micro- and mesopore regions, indicating microporous sites are connected to the mesopore channels. However, few mesoporous sites are observed due to the pore blocking by hydrocarbon chains for 3 nm samples. For a larger pore of 30 nm, the pore size is reduced for the modified silica (C_{10} -30 nm).

By obtaining data at very low partial pressure of HP xenon in a flowing mixture (1% of total, or ~ 10 mbar) the contribution from Xe–Xe interactions becomes negligible, and the spectra can be considered as characteristic of the framework and the surface. The very low xenon concentration also effectively reduces the rate of exchange between the different adsorption regions, which makes it possible to detect inhomogeneity in the pore space of the materials. Together with the fact that N_2 adsorption and TEM data show well ordered nanoporous channels,⁶³ such a broad distribution of chemical shifts is unlikely to be the result of non-uniformity of the mesoporous channels for this material. It is more likely to be a consequence of inhomogeneity in the structure and porosity of the materials particles on the micrometre scale. Therefore, variable temperature ^{129}Xe NMR can be used to detect the imperfection or surface defects (made of micropores) of the ordered pore channels.

8.2.2 Polymer Aerogels

HP ^{129}Xe NMR has been used in the studies of porosity and connectivity of porous polymers including polymer aerogels.^{15,16,31,34,48–51} Aerogels represent a class of novel open-pore materials with high surface area and nanometre pore sizes. They exhibit very low mass densities, low thermal conductivity, good acoustic insulation, and low dielectric constants. The materials have potential applications in catalysis, advanced separation techniques, energy storage, environmental remediation, and as thermal insulators. Polymer aerogels are stiffer and stronger than silica aerogels and are better insulators with higher thermal resistance. Resorcinol-formaldehyde (RF) aerogels were prepared through the base-catalyzed sol-gel polymerization followed by drying in supercritical CO_2 .^{85,86} The

[resorcinol]/[catalyst] (R/C) ratio of the starting sol-gel solution was found to be the dominant factor that affects the properties of RF aerogels. Since the unique microstructures of aerogels are responsible for their unusual properties, characterizing the detailed porous structures and correlating them with the processing parameters are vital to establish rational design principles for novel organic aerogels with tailored properties.

The use of HP xenon is critical in ^{129}Xe NMR studies of aerogels because the extremely low densities of aerogels and very long ^{129}Xe relaxation times would otherwise result in very low signal intensities. Variable temperature ^{129}Xe NMR and 2D EXSY were used to obtain a better understanding of the pore structure, the uniformity of the adsorption regions, and the interconnectivity between different adsorption regions.^{15,16} Figure 8.2a displays a representative spectrum for RF with $R/C=300$. On the basis of the magnitude of the chemical shifts (CS) and variation of the shifts with the temperature (not shown), the broad signal at 140 ppm was attributed to the micropores formed by agglomerated polymer particles and a narrow signal at 90 ppm to the mesopores. ^{129}Xe 2D EXSY spectra (Figure 8.2 b–d) reveal the interconnectivity between different adsorption regions. The homogeneity of distribution of the mesopores in the aerogels can be tested directly using CF ^{129}Xe chemical shift imaging,⁸⁷ as shown in Figure 8.2e. The evenness of the profile clearly indicates uniformity of distribution of the mesoporous spaces throughout the bulk of aerogel. The volume-to-surface-area ratios (V_g/S) derived from the temperature dependent chemical shift data were found to show a very strong correlation with the R/C ratios. These previous studies^{15,16} have demonstrated that HP ^{129}Xe NMR is an ideal means for assessing the volume-to-surface-area (V_g/S) ratios of mesopores in polymer aerogels without using any geometric models. Both this ratio and the Xe exchange data provide important insights into the geometry and the interconnectivity of the nano- and mesoporous spaces in these soft materials. Once again this demonstrates the power and complementarity of HP ^{129}Xe NMR spectroscopy *versus* conventional techniques in providing new insights into pore structure.

8.2.3 Hierarchically Ordered Mesoporous Materials

Biological systems, even primitive ones such as diatoms, made mainly of amorphous silica, exhibit forms with highly ordered hierarchical organization. Considerable efforts have been devoted to develop synthetic materials with multi-scale structural ordering similar to that in natural materials.^{88–102} Since these materials with nano- to macro-scale ordering have the advantage of multiple pore-size regions, they are excellent candidates for many technologically important applications including catalysis, adsorption, separation, mass-transportation, bioengineering and environmental science.

HP ^{129}Xe NMR has been used for probing the porosity of hierarchically ordered mesoporous materials, including wood replicas.^{17,22,26,36} Wood is a natural composite material and consists chemically of cellulose,

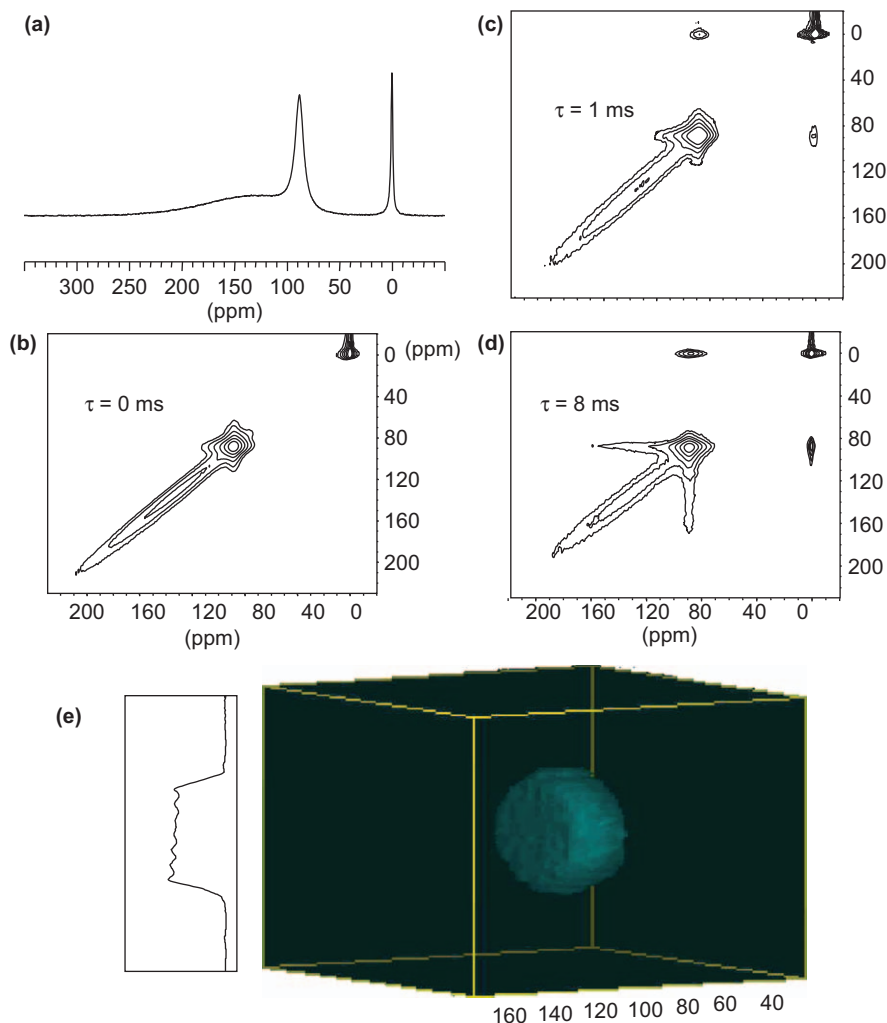


Figure 8.2 (a) CF HP ^{129}Xe NMR spectra for RF aerogels prepared with an R/C ratio of 300. (b)–(d) CF HP 2D EXSY ^{129}Xe NMR spectra for RF aerogels ($R/C = 300$) recorded with τ as indicated. All spectra were obtained at 293 K with a HP Xe flow rate of 45 sccm. (e) CF ^{129}Xe chemical shift image of Xe in cylindrical block of RF aerogel ($R/C = 300$). Intensity profile shown on the left is taken through the center of the image.

hemicelluloses, and lignin. Microscopically, wood tissues contain interconnected cells (tracheas) and open spaces (lumens), forming a wide range of stable structures as shown in Figure 8.3. They are ideal as templates for the synthesis of inorganic materials with both structural and morphological complexity. The synthetic hierarchically ordered ceramic materials not only reproduce the cellular structures of the biological tissue entirely, but they

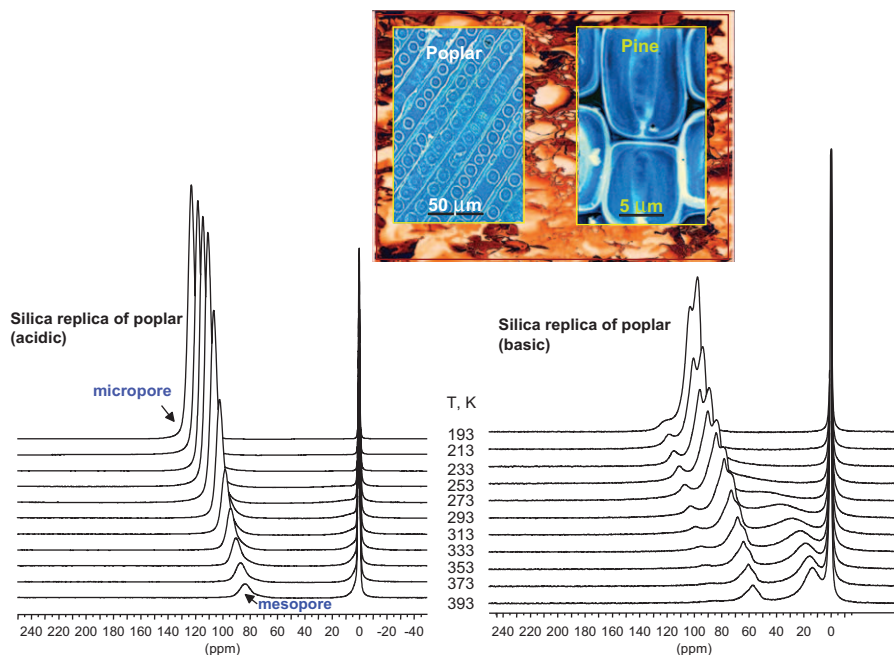


Figure 8.3 ^{129}Xe NMR spectra obtained at various temperatures with a continuous flow of hyperpolarized xenon adsorbed in samples of mineralized wood of different preparations: poplar treated under acidic conditions (left), poplar treated under basic condition (right), the SEM images of wood showing hierarchically ordered porosity (top).

also contain organized nanoporous channels in the cell walls. The entire sample, including interconnected cells, pit structures, multi-layered cell walls, and even oriented fibrous features, was well preserved after all of the organic contents had been removed by heating.

The ^{129}Xe NMR spectra recorded as a function of temperature for the calcined silica replicas of poplar prepared at different pHs are shown in Figure 8.3.¹⁷ The wood replica prepared under acidic conditions show rather narrow and relatively symmetric lines throughout the temperature range, indicating homogeneity of environment, a rather narrow distribution of mesopore sizes, and easy exchange among different pore spaces. However, many lines observed in the ^{129}Xe NMR spectra for samples prepared in basic media are the result of inhomogeneity and rather broad distributions in the size of the pores. ^{129}Xe NMR spectra clearly indicate the difference in structure and connectivity of the pores for the silica replica of poplar under acidic and basic conditions. The variation in structure and connectivity of the pores is attributed to the different mechanisms for the formation of positive and negative replicas under different pHs. Under acidic conditions, the silica precursors are hydrolyzed and condensed onto the cell wall leaving the majority of the void spaces and pits unoccupied, thus resulting in the

formation of positive replicas. In contrast, because of the fast condensation under basic conditions, the silica precursors clog the cells and pit structures, shutting off the communication channels between cells. Although TEM micrographs show hexagonally ordered 20 Å pores for both silica samples of positive and negative replicas, ^{129}Xe NMR data clearly provide a more complex picture. Similar to TEM, the ^{129}Xe NMR results indicate pores of similar sizes for all samples. However, because the length scale of ^{129}Xe NMR is significantly large than TEM, μm as opposed to nm, it provides some complementary results to the TEM information. On another hand, the effective length on the order of microns is about the size of a single wood cell (5–100 μm), and the seeming differences between ^{129}Xe NMR data for different samples should be viewed mostly as differences in the larger, cell-size voids.

8.2.4 Infiltrated and Doped Mesoporous Materials

Infiltrating or doping chemical species into the porous channels produces modified mesopores with enhanced properties. HP ^{129}Xe NMR has been successfully applied to these materials, including ammonia borane infiltrated into mesoporous silica.^{12,19,38} Ammonia borane (AB) infiltrated into the mesoporous channels (illustrated in Figure 8.4) showed enhanced kinetics for reversible hydrogen storage relative to the bulk materials.¹² One advantage of the porous scaffolds is the potential to preserve the nanophase properties through several cycles of hydrogen uptake and release. However, the benefits are at the expense of the added weight and volume of the scaffold leading to a decrease in the available hydrogen. It was found that temperature onset for hydrogen release depended on the loading level of AB infused in mesoporous silica above a 1:1 weight-to-weight ratio.¹⁰³ It is important to know how the AB resides in porous channels of silica at different loading. Unfortunately conventional experimental techniques such as BET and TEM fail to provide direct insight into the observed phenomena as a function of AB loading in silica. BET doesn't provide reliable results for all AB coated MCM samples because a relatively high vapor pressure of AB prevents accurate measurements. TEM is not successful at imaging the ammonia borane in the scaffold as a result of weak scattering of electrons by the light elements B and N.

Variable-temperature HP ^{129}Xe NMR measurements have been systematically carried out on a series of MCM-41 materials with AB loading ranging from 33 to 75 wt% (1:2 to 3:1 AB:MCM).

Figure 8.4 displays the spectra plotted together for four samples at 283 and 243 K for a better visualization of different pore environments in AB:MCM materials. Three different pore environments for AB in MCM41 at four loading levels are visible: pristine mesoporous channels in MCM41; mesoporous channels coated with AB; and pores formed by interparticle spacing due to the excessive AB aggregated outside the MCM meso-channels. As compared with TEM and BET that show no distinction between 1:1 and

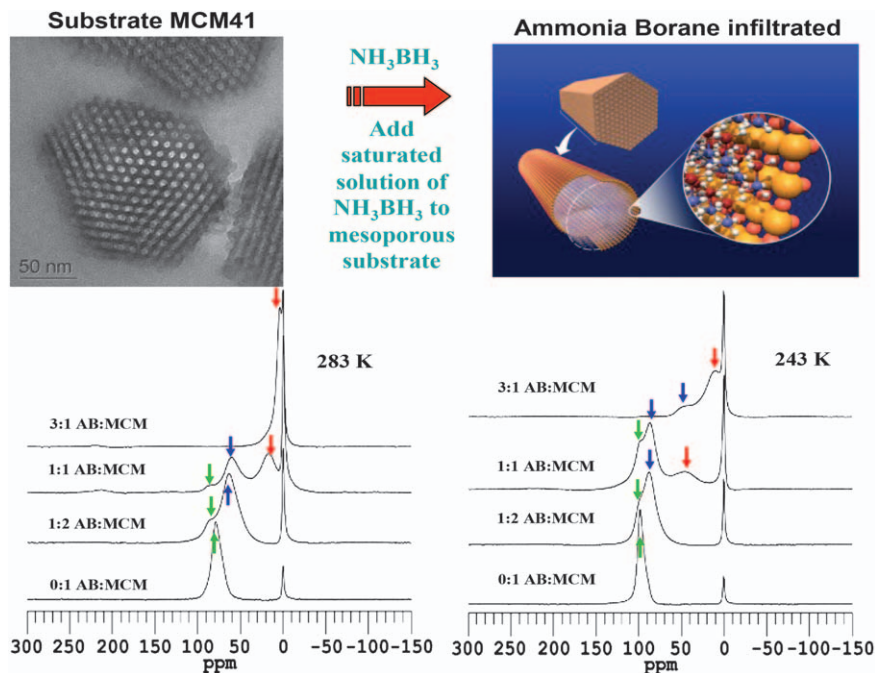


Figure 8.4 A schematic illustration of preparation for ammonia borane (AB) infiltrated into the mesoporous silica along with the HP ^{129}Xe NMR spectra taken for 0:1, 1:2, 1:1, and 3:1 AB-MCM materials at 283 and 243 K, respectively. Peaks are assigned to pristine mesoporous channels in MCM (green arrows); mesoporous channels coated with AB (blue arrows), and interparticle spacing due to the excessive AB aggregated outside the MCM meso-channels (red arrows).

3:1 AB-MCM, the study on AB:MCM has demonstrated that variable-temperature HP ^{129}Xe NMR can be used to detect different local pore environments that otherwise are indistinguishable by other pore characterization techniques. At a relatively low AB loading at 33% (1:2 AB:MCM), no excessive AB particles are observed in Figure 8.4, indicating that all AB are infused into the mesopore channels. With an increase in the loading to 50% (1:1 AB:MCM), the excessive AB particles deposited outside the mesoporous channels were observed, suggesting a sequential deposition process where AB is first infiltrated into the mesoporous channels and then starts to deposit outside the channels. It is understandable that AB prefers the mesoporous channels because of the capillary effect of these nanosized porous channels. With a further increase of the loading to 75% (3:1 AB:MCM), more AB are deposited outside the mesoporous channels as shown in Figure 8.4 where a large resonance peak at near 0 ppm associated with the excessive AB outside the meso-channels is observed at 283 K. However, the resonance peak representing AB inside the meso-channels is only visible at temperatures below 243 K, indicating that HP

^{129}Xe NMR is a powerful technique for probing these partially blocked pores that could otherwise not be discerned by other pore characterization techniques such as TEM and BET. Furthermore, from the variable-temperature NMR spectra it was found that a fraction of the surface area inside the mesochannels has more than one monolayer coating of AB and three different types of pores in AB:MCM are connected. Such detailed information on how supported AB resides in nanoporous channels and how it evolves with increase of AB loading level is important for designing novel materials with optimal hydrogen storage and release properties.

8.2.5 Porous Electrode Materials

There has been on an increased interest in developing hybrid nanostructured materials with controlled porosity for electrochemical energy storage and other energy related applications. The extent of interconnectivity between nano- or mesopore domains in such materials markedly affects their transport properties. Therefore, characterization of resident porosity and pore interconnectivity is key to better understanding ion transport mechanisms in nanoporous materials.

Hyperpolarized (HP) ^{129}Xe NMR has been used to probe the porosity and interconnectivity of pores in porous electrode materials including TiO_2 as anode materials in Li ion batteries.^{10,13} TiO_2 is studied because it is an abundant, low cost, and environmentally benign material. It is also structurally stable during Li insertion/extraction and is intrinsically safe through retardation of electrochemical deposition of lithium. These properties make TiO_2 particularly attractive for large-scale energy storage. An approach to improve Li-ion insertion properties invokes substitution of hybrid nanostructured electrodes that combine nanostructured electrode materials with other conductive additive nanophases. To improve high-rate charge/discharge performance and reduce the cost of electrochemically active materials, it is important to identify high surface area, inexpensive, and highly conductive nanostructured materials that can be integrated with electrochemically active materials at the nanoscale. It was found that a nanostructured TiO_2 -graphene hybrid material prepared by means of an anionic surfactant mediated self-assembly growth process further increased the Li ion insertion rate and capacity.¹⁰

A series of HP ^{129}Xe NMR spectra were taken under nearly identical conditions for both pure mesoporous TiO_2 and hybrid TiO_2 -FGSs (functionalized graphene sheets). Figure 8.5 displays the HP ^{129}Xe NMR spectra taken at 298 K for pure mesoporous TiO_2 , self-assembled rutile TiO_2 -FGS hybrids, and pure bulk functionalized graphene sheets (FGSs), respectively. Two distinct chemical shifts observed for meso-1 and meso-2 shown in Figure 8.5 indicate that there are at least two different types of pores or regions in pure mesoporous TiO_2 . Since the XRD and TEM show the same TiO_2 composition across the bulk sample of this material, the difference in chemical shift data for meso-1 (at 63.7 ppm) and meso-2 (at 73.9 ppm) is

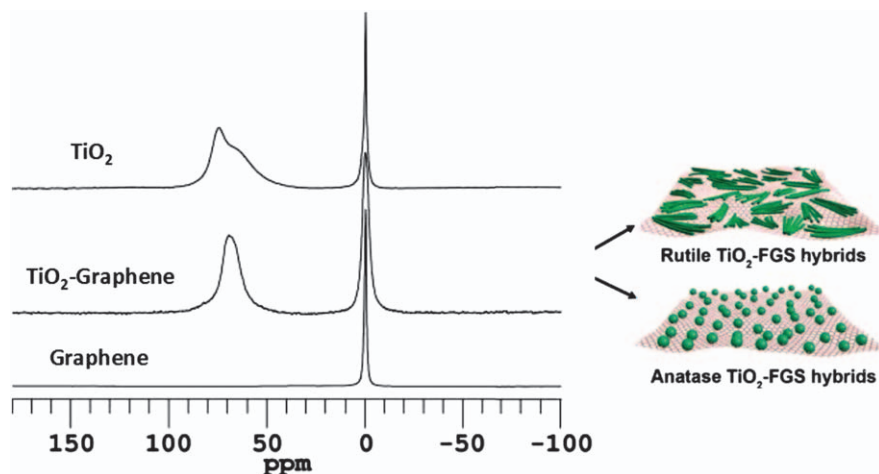


Figure 8.5 HP ^{129}Xe NMR spectra taken at 298 K for TiO_2 -FGS hybrid material, pure mesoporous TiO_2 , and pure bulk FGS, respectively, along with schematic drawing of the anionic sulfate surfactant-mediated stabilization of graphene and growth of self-assembled TiO_2 -FGS hybrid nanostructures. The green rods represent the rutile phase nanorods, while the planar purple mesh corresponds to the individual graphene sheet.

most likely due to the difference in geometries and/or sizes of the pores. TEM and XRD data have provided evidence that the majority of the mesopores in TiO_2 particles are made from the orientation of crystalline rutile TiO_2 nanorods with a small amount of anatase TiO_2 particles aggregated at the ends or on the surface of a bundle of rutile nanorods. It was also found from the ^{129}Xe NMR spectra that the peak area for meso-1 in Figure 8.5 is significantly larger than that of meso-2 pores. Therefore, based on the ^{129}Xe NMR data supported by TEM and XRD data it is reasonable to assign the meso-1 to the mesoporous channels comprised of rutile TiO_2 nanorods and the meso-2 to the mesopores formed from the aggregated anatase nanoparticles. Although the chemical shift for meso-2 is larger than that for meso-1, we obtained similar pore sizes because of the difference in pore geometries. The pore diameter of 3–4 nm for meso- TiO_2 determined from the ^{129}Xe NMR data is in agreement with the TEM and BET results. Unlike BET, ^{129}Xe NMR allows identification of pores of similar size in different phases of TiO_2 .

Interconnectivity between meso-1 and meso-2 has been evaluated using 2D EXSY spectra for pure mesoporous TiO_2 . The experiment was performed under flow conditions so the results can only be interpreted in purely qualitative terms. Figure 8.6 displays the 2D EXSY spectra with mixing times of 5 ms and 15 ms. The cross peaks show exchange takes place between both adsorption sites and the free gas. With mixing times as short as 5 ms the exchange has already taken place between both types of pores and the free gas, indicating that these two types of pores are well connected.

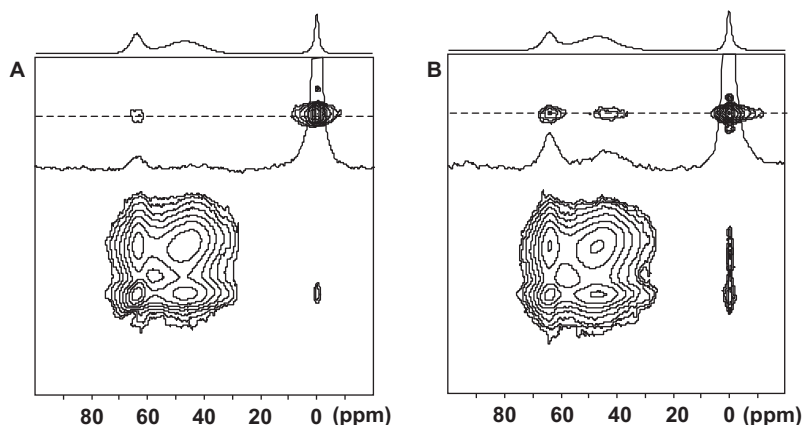


Figure 8.6 2D EXSY spectra of HP ^{129}Xe in mesoporous TiO_2 under continuous flow conditions at 313 K and mixing times of 5 ms (A) and 15 ms (B). Positions of 1D cross-sections of the spectra shown in insets are indicated by the dashed lines.

The previous HP ^{129}Xe NMR studies^{10,13} of TiO_2 porous electrode materials have demonstrated that ^{129}Xe NMR is a powerful technique for probing any changes in porosity and interconnectivity of the pores caused by the addition of a small amount of functionalized graphene sheet (1 wt%) into the network of mesoporous TiO_2 . The information on the interconnectivity of the pores is critical for understanding transport properties in porous materials.

8.3 Conclusions and Perspectives

Structures, interconnectivity and functionality in porous materials play an important role in controlling properties of materials. HP ^{129}Xe NMR has been proven as a powerful tool for probing structures, interconnectivity and functionality in porous materials. 2D-EXSY of HP ^{129}Xe NMR is useful for obtaining the information on the interconnectivity of pores, unlike other techniques such as small angle X-ray, neutron scattering, and gas absorption that do not provide direct information on how channels and cages are connected.

HP ^{129}Xe NMR has been applied to many classes of mesoporous materials including (a) functionalized ordered mesoporous materials; (b) polymer aerogels; (c) hierarchically ordered mesoporous materials; (d) infiltrated and doped mesoporous materials; and (e) porous electrode materials. As new materials are discovered, the needs for HP ^{129}Xe will increase. It is expected that HP ^{129}Xe NMR will be more widely used in materials sciences due to its unique capability of probing porosity and interconnectivity of the pores. The enhanced polarization rate of HP ^{129}Xe NMR polarizer enables the future studies of materials with relatively low surface area, thin porous membranes and self-assembly structures in solution. One of the emerging topics in

materials sciences is to study the structure and property relationship for novel electrode materials in order to have rational design for the next generation of efficient batteries. Preliminary results⁵⁶ suggested that the binder has a large effect on the porosity of the electrode materials, and ^{129}Xe NMR signal is extremely sensitive to the initial SEI (solid electrolyte interface) growth. Although the practical electrode is made of several components, the initial study showed that HP ^{129}Xe NMR can be a powerful diagnostic tool to any changes in porosity or surface compositions during the electrochemical reactions, proving the feasibility for future *in situ* ^{129}Xe NMR measurements of practical electrode materials.

Acknowledgements

The author is supported by the EPSCoR Implementation Grant DE-SC0007074, Office of Basic Energy Sciences, U. S. Department of Energy (US DOE). The author thanks Dr. I. L. Moudrakovski, Prof. Brian Saams, Ting Liu and Dr Myeonghun Song for the help.

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Porous Materials Explored by Hyperpolarized Xenon NMR

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9.1 Introduction

Xenon NMR spectroscopy is extremely informative on the structure of micro- and mesoporous materials.^{1–3} The sensitivity of ^{129}Xe NMR can be enhanced by orders of magnitude by the laser-assisted hyperpolarized technique (HP) that produces a significant xenon signal even at very low concentrations.^{4,5} By the continuous flow (CF) technique, hyperpolarized Xe can be continuously delivered to the sample allowing the recording of 2D exchange spectra and collecting information on the accessibility of the nanochannels.⁶ This technique, sensitive to the empty spaces in the material, combined to multinuclear 1D and 2D solid-state NMR experiments, can work synergistically to give a complete picture of porous materials which possess the double feature of being impermeable and solid in their walls as well as accessible to gas species. Indeed, it enables definition of the nature of the pore walls, the dimension and, possibly, the shape of the space available to the diffusing gases. Moreover, it is a noninvasive technique and does not affect the crystal structure. Thus, xenon is a direct and unique probe of pore structure (channels or galleries) and mimics the behavior of guest atoms or molecules that can be confined therein. In this overview we touch on several aspects of

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

© The Royal Society of Chemistry 2015

Published by the Royal Society of Chemistry, www.rsc.org

HP xenon experiments in porous materials through the description of a few case-studies representative of the main families of organic and hybrid porous substances. Fully inorganic and conventional zeolitic materials will be neglected.

9.2 Porous Molecular Crystals

The challenge of preparing Porous Molecular Crystals (PMCs) started in a rational way in 1999–2000, when it was demonstrated that even molecular crystals assembled by van der Waals interactions could form materials with permanent porosity.^{7,8} The existence of these crystals is in sharp contrast with the principle of the maximum occupation of the space by the crystal-lizing molecules, in other words the principle of close-packing of a molecular crystal.⁹ HP ^{129}Xe NMR played an important role in providing the ultimate proof of the ‘zeolitic’ nature of the molecular crystals, showing reversible and quick uptake/release of atoms and molecules from the gas phase.¹⁰ A prototype of this family, tris-*o*-phenylenedioxy-cyclotriphosphazene (TPP) stimulated, during the following decade, further efforts in preparing gas-absorptive molecular crystals. This inspired challenging projects for new benchmarks of high pore capacity and surface area PMCs,^{11–13} which makes them more and more competitive with porous MOFs and PCPs.^{14,15} The demonstration of diffusion of hyperpolarized xenon into the crystal channels, combined with XRD, MAS NMR and DSC evidences, paved the way to the studies of greenhouse gases, such as carbon dioxide, and for energy supply as methane and hydrogen in PMCs.^{16,17}

The methodology used to produce crystals endowed with permanent porosity was based on the choice of a host of suitable shape and symmetry to grow crystalline inclusion compounds that contain guest molecules aligned in channels, followed by a slow and mild evacuation of the volatile guest. TPP microcrystalline powder prepared in this way underwent exploration by hyperpolarized xenon. The channel hexagonal cross-section of about 0.5 nm is close in size to the xenon atom diameter (Figure 9.1). Therefore, the immediate surroundings perceived by xenon during its exploration of the channels are mirrored in the ^{129}Xe NMR chemical shift due to interactions with channel walls and with the next neighboring xenon atoms in the channels. These unbalanced interactions could be imprinted in the anisotropic spectral profile. Primarily, the hexagonal symmetry of the channels generated an axially symmetric lineshape ($\eta \cong 0.1$). The axial-symmetry profile persisted at any observation temperatures, although the sign of $\Delta\delta$ (where $\Delta\delta = \delta_{\parallel} - \delta_{\perp}$) associated to xenon in the confined state changed remarkably as a function of temperature and partial pressure; the only exception being the isotropic signal observed at the inversion points of the anisotropy sign, where the three orthogonal tensor components coincide.¹⁰

Higher pressure and lower temperature were shown to act in parallel, and chemical shift anisotropy (CSA) exhibits a negative sign. This was explained by the accumulation of xenon atoms in the channels augmenting the

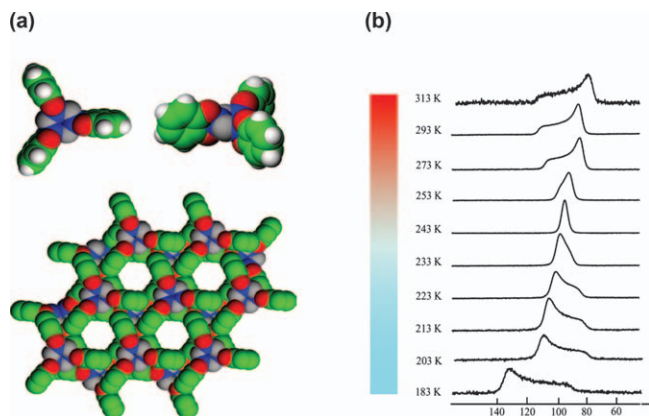


Figure 9.1 (a) Crystal structure of TPP in the nanoporous hexagonal modification. (b) CF HP ^{129}Xe NMR of Xe (2% concentration in He) flowing in the TPP hexagonal phase at variable temperature.

contribution of xenon–xenon interactions, while down to the limit of low xenon concentration and high temperature the only confining interactions came from the channel walls. Xenon loaded in the channels at variable xenon pressure was described by xenon isotherms, which offer key data for understanding the chemical shift as a function of xenon–xenon collision frequency. Collectively, these results provided a neat example of modulation of an axial anisotropic profile by feeding or depleting the observed xenon atom from its next neighbors.

9.2.1 Single Crystals

The use of organic single-crystals is attractive in the field of oriented materials and allows for ordered alignments of pores and surfaces. Porous single-crystals combine absorption and anisotropic diffusion properties. Confinement within restricted spaces by the use of oriented porous materials is the method of choice for obtaining the orientation of gases trapped in solids because it can imprint its anisotropy on a gas and manipulate the spatial orientation of a gas with respect to the main magnetic field. This was made possible by encapsulating xenon gas in a TPP single-crystal with permanent porosity and observing the xenon NMR resonances as a function of the orientation of the single-crystal. Hyperpolarized ^{129}Xe NMR, due to its high sensitivity, opened up a way to collect xenon NMR signals from porous single-crystals.¹⁸

Porous single-crystals of TPP could be grown to the size of a few millimetres and exposed to a continuous flow of hyperpolarized xenon at 2% concentration in helium; a single intense signal was detected far downfield with respect to that of the free gas at 0 ppm (Figure 9.2). The *c*-axis of the crystal was inclined at variable θ angles, from 0° to 90° with respect to the main magnetic field, and a spectrum was acquired at each given inclination. The resonances move progressively from downfield to upfield spanning 31 ppm. The limits of the chemical-shift values at 111.9

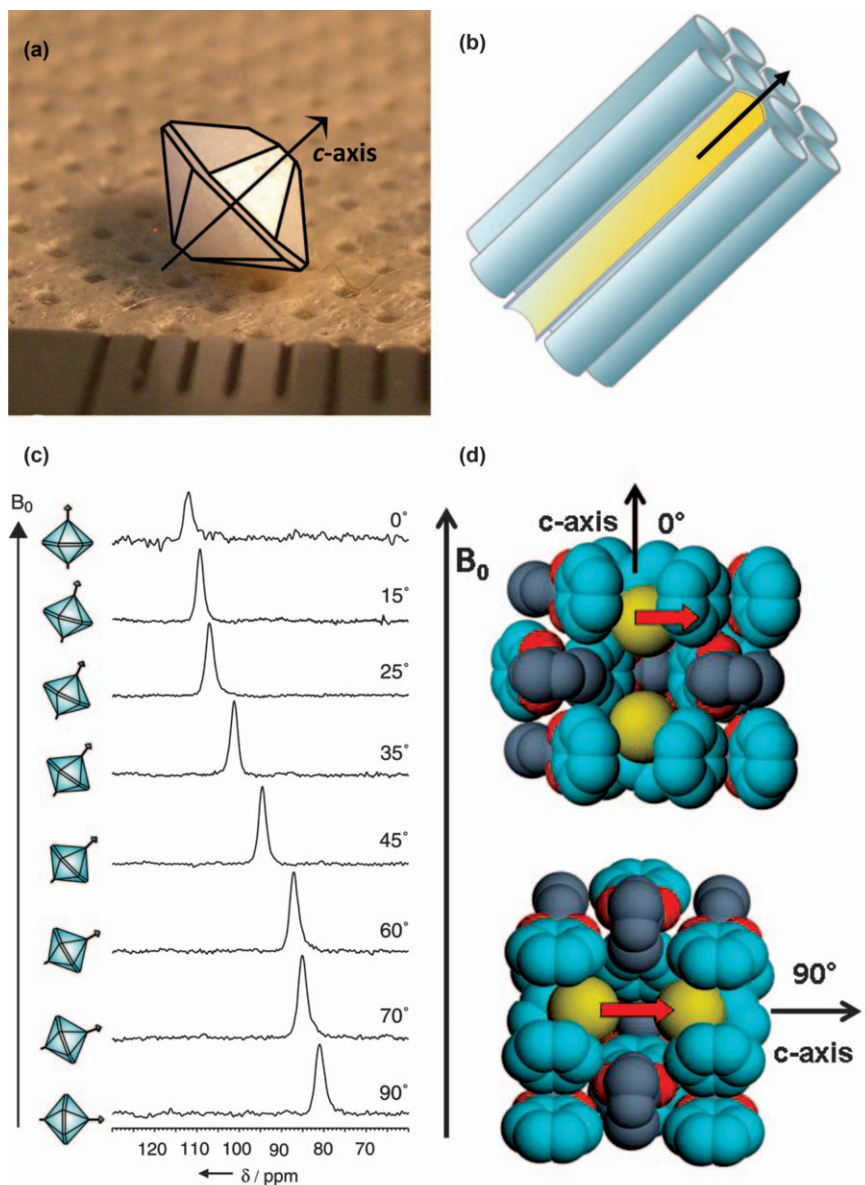


Figure 9.2 (a) Porous molecular single-crystal of TPP viewed perpendicularly to the *c*-axis. (b) Sketch of the independent and parallel nanochannels aligned with the same alignment as in (a). (c) Continuous flow hyperpolarized ^{129}Xe NMR spectra of the porous molecular single-crystal inclined at variable orientations from 0° to 90° with respect to the main magnetic field. The axial symmetry of the shielding tensor is in agreement with crystal symmetry, and the tensor δ_{zz} component, detected at a θ angle of 0° , coincides with the *c*-axis of the crystal. (d) Nanochannels oriented at 0° and 90° with respect to B_0 . Xe atoms are highlighted in yellow. The red arrows indicate the xenon-wall and xenon-xenon interactions.

and 80.9 ppm for θ angles of 0° and 90° , respectively, indicated the entity of xenon–wall and xenon–xenon interactions: in fact, the component of the xenon tensors which is effective on the recorded resonances is perpendicular to B_0 , as depicted in Figure 9.2. On the contrary, the crystal rotation about the c -axis does not affect the chemical shift, according with the hexagonal symmetry of the crystal structure which generates virtually cylindrical channels.

The interaction distribution produced by the crystalline channels on Xe atoms resulted in an anisotropic xenon electron distribution and xenon changed from the spherical symmetry of the free gas, with the three main components of the tensors being equal to an anisotropic shape with axial symmetry. The presence of a single resonance in each spectrum indicates that all xenon nuclei experienced the same environment, and neither different sites for xenon nor twinning of the crystal were present. Thus, the main components of the xenon shielding tensors were recognized unambiguously and assigned to the crystal reference system, independently of crystal morphology. Furthermore, the limit of extreme dilution of xenon that was used in the highly sensitive hyperpolarization experiments permitted magnetic parameters of isolated xenon nuclei in the restricted space of the nanochannels to be obtained, without spurious contribution of xenon–xenon interactions. The interaction energy of 23 kJ mol^{-1} , calculated at low xenon loading, was explained by the favorable topology of the channel walls offering multiple van der Waals interactions to the guest atom. At the two limits of crystal orientation θ of 0° and 90° , the parallel and perpendicular components of xenon anisotropy could be singled out, and they showed a very marked dependence on temperature (Figure 9.3).

When the channels were oriented perpendicular to the magnetic field the chemical shift moved downfield with decreasing temperature (from 80.0 ppm at 313 K to 109.6 ppm at 212 K). This is due to increasing interactions with other neighboring xenon atoms along the channels, since at lower temperature the concentration of absorbed xenon increases considerably, affecting the δ_{xx} (or δ_{yy}) component of the shielding tensor. In fact, the xenon absorption isotherm at 210 K demonstrates a high Xe occupancy of 0.7 xenon moles per mole of host at operating conditions of 15.2 Torr indicating about 70% of the full loading of the channels.

From the crystal structure, a complete filling is reached at 1:1 xenon mole per host mole. The downfield shift was confirmed by performing the experiment at room temperature with the same crystal orientation but at increasing xenon concentrations: a de-shielding of about 4 ppm has been observed for the increase in xenon concentration from 2% (15.2 Torr) to 4% (30.4 Torr). When the crystal was set with the nanochannels aligned parallel to the main magnetic field, the chemical shift of the δ_{zz} component changed from 115.4 ppm at 313 K to the upfield value of 82.7 ppm at 212 K. Since at this orientation the resonance is insensitive to xenon concentration,^{19,20} the change in chemical shift is totally due to the interactions of xenon with the channel walls.

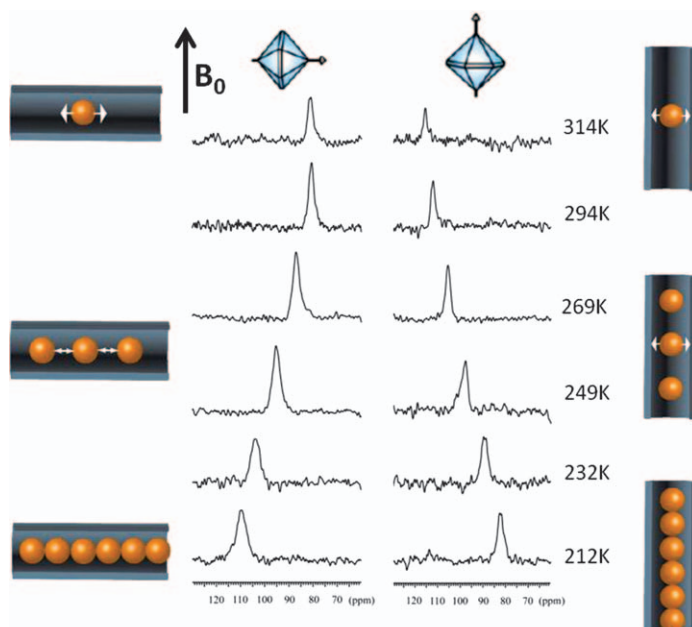


Figure 9.3 Variable temperature continuous flow hyperpolarized ^{129}Xe NMR spectra of a porous molecular single-crystal inclined at two orientations θ of 90° (left) and 0° (right) with respect to the main magnetic field.

The upfield shift at low temperature indicates that xenon atoms experience weaker interactions with the walls, which are balanced by stronger interactions with neighboring xenon atoms. Thus, it was possible to observe macroscopically aligned chains of xenon atoms librating about the center of the crystalline channel. The organization of xenon atoms in single rows offered the opportunity to manipulate the orientation of Xe chains in the macroscopic space. These observations provided the experimental data for comparison to the theoretical predictions of the chemical shift dependence on the xenon–xenon and xenon–wall collisions.^{19,20}

Furthermore, a collection of randomly oriented single-crystals of distinct sizes and morphologies was set in the main magnetic field and exposed to the hyperpolarized xenon stream. Separate lines could be detected simultaneously and, from the knowledge of the angular dependence of the chemical shift from the orientations, it was possible to establish the angular configuration of this unknown distribution of crystals. Based on the high resolution, for angles within 15° and 75° the NMR determination of the orientation angles could be measured with an accuracy of 1° .

Therefore, HP ^{129}Xe NMR observation of single-crystals showed the feasibility to transfer anisotropy from a host to a gas traveling along the parallel tunnels. In practice, it opens up the possibility of describing the

orientation of the cavities in confining materials and leads to the recognition of specific access surfaces on crystal faces.

In addition to the measurement of CSA, which provides information on the shape of the cavity, HP ^{129}Xe NMR in the continuous flow mode can quantify polarized xenon uptake per time unit and consequently diffusion coefficients in the materials. In the case of crystals with narrow pipes, xenon atoms are not allowed to bypass one another and thus each atom has to wait for the advancement of the next atom in line to move on. This condition of limited diffusive freedom is indicated as 'single-file diffusion'. Indeed, this diffusive condition is really constrictive, similarly to what was imagined to happen for the inhabitants of Line-Land,²¹ and diffusion is much slower for a new-entry atom when channels are partly occupied. By CF HP ^{129}Xe NMR spectroscopy, slow diffusive phenomena and diffusion times in the range of seconds could be measured. In fact, the feed chamber supplies continuously polarized xenon, that, after a train of 90° pulses (which resets the magnetization to zero), accumulates into the pores according to the diffusion rates. The signal build-up was followed with time and signal intensity dynamics recorded at variable temperature. The perfect fit indicated that the model of the single-file diffusion, slower than the conventional mono-dimensional diffusion, was operative under a wide range of conditions.²²

9.2.2 Porous Dipeptide Crystals

Porous molecular crystals of biological origin, sometimes named biozeolites, possess extended channels in their crystalline structures, available for gas diffusion, storage and separation.^{23,24} Xenon, as happened commonly in other PMCs, was the first spy to report information about the shape of the cavities in the crystal structure. An extensive experimental and theoretical work performed during the nineties, collected abundant details on dipeptide crystals.^{25,26} The work on xenon NMR was preliminary to the first observation of CO_2 and CH_4 capture in crystal of biological origin.^{17,27} Moreover, the diffusion of monomers in dipeptide crystals permitted them to be envisaged as reaction vessels for inclusion polymerization.²⁸ The main interest for the study of biological PMCs derives from the peculiar feature that they can exist in a variety of structures with different pore size and helicity within a given family.²³ This resulted in a large diversity of chemical shift values observed as a function of the channel constriction; moreover, a large CSA could be recorded in a few cases.²⁹ Also, porous crystals of L-Ala-L-Val (AV) and L-Val-L-Ala (VA) with a controlled mean lengths of 50–100 μm were used to test single file diffusion behavior in the narrow channels of crystalline dipeptides, as already shown in the case of TPP. Pulsed field gradient NMR and hyperpolarized ^{129}Xe spin tracer exchange NMR could confirm single-file diffusion, with mobility factors of around $5 \pm 0.7 \times 10^{-13} \text{ m}^2 \text{ s}^{-1/2}$.^{30,31}

9.3 Organo-modified Clays

Phyllosilicates are synthetic or naturally occurring materials which show the common structural features of being composed of covalent layers intercalated by a soft layer of exchangeable ions.³² By replacement of those ions with charged organic molecules or surfactants, such as alkyl-ammonium salts, organo-modified phyllosilicates are produced. ^1H - ^{13}C HETCOR 2D NMR with hydrogen decoupling provided direct proof of the intimate relationships between the organic and inorganic components at the hybrid interfaces. These hybrid compounds are useful for interacting with polymers to yield reinforced composites by intercalation or exfoliation.^{33,34}

On the other hand, the intercalation by globular organic ions generates pillars to counterbalance the surface charge and the interlayer space is filled only by a limited amount of them, originating a notable porosity to be accessed and explored by xenon atoms. Considering the 6 Å diameter of the cations, which act as pillars, the height of the galleries between the inorganic lamellae is congruent, as derived by XRD. However, the direct observation and measurement of the void spaces available after organic pillaring is substantially inaccessible by any other spectroscopy than xenon NMR.

In a representative example, a tetraethylammonium intercalated hectorite (TEA-hectorite) adduct was placed in a homogeneous magnetic field through which there is a continuous flow of hyperpolarized Xe; after a few scans an intense resonance of xenon diffused inside the slit pores was collected (Figure 9.4).^{35,36} At room temperature the signal at 105 ppm, downfield from the free-gas resonance, is indicative of the gas confined to the restricted spaces. Such a high value falls within the chemical shift range observed for microporous materials investigated in the limit of diluted xenon. In the case of hyperpolarized xenon experiments, the concentration was as low as 1.25% with a partial pressure of 9.5 Torr. At the diluted limit, the Xe-probe samples the interaction with the surrounding surface, with the advantage that the Xe-Xe interactions become negligible. Under these conditions the chemical shift δ_s due solely to interactions with the surfaces, depends on the mean free path L that defines the size of the explored micropores as $\delta_s = 243 \times 2.054 / (2.054 + L)$, according to the semiempirical model proposed by Fraissard and tested mainly on zeolites.³⁷ Taking into account the xenon diameter, the pore size is evaluated as 7 Å. This is consistent with the interlamellar spacing generated by the pillars in the clay, as determined by X-ray diffraction, and indicates that the ammonium pillars are effective in restricting the in-plane movement of xenon within a space of about 7 Å. Moreover, from the HP Xe NMR data the average microscopic space of the void was measured: indeed the lateral void is twice as large as the space occupied by a single ammonium pillar, indicating that a remarkable 70% of the total interlamellar volume could be accessed by the adsorptive species. Xe resonance shifted linearly downfield by lowering the temperature, up to 144 ppm, indicating increasing condensation on the micropore surface. Below 205 K an extra resonance

appeared, due to xenon condensation on the particles' external surfaces that competed with sorption within the micropores (Figure 9.4).

The easy accessibility of the galleries created by the ammonium pillars was demonstrated by the fact that the signal of the confined xenon was recorded in less than 200 ms. In addition, the lipophilic nature of xenon allowed favorable interactions with organic TEA even in the extreme dilution of 1.25% of the gas mixture. The overall adsorption energy of xenon in the galleries amounts to 14 kJ mol^{-1} . The porosity generated by pillared cations, as demonstrated by HP Xe NMR, was later exploited for the adsorption of small organic molecules and gases. This was tested successfully by benzene

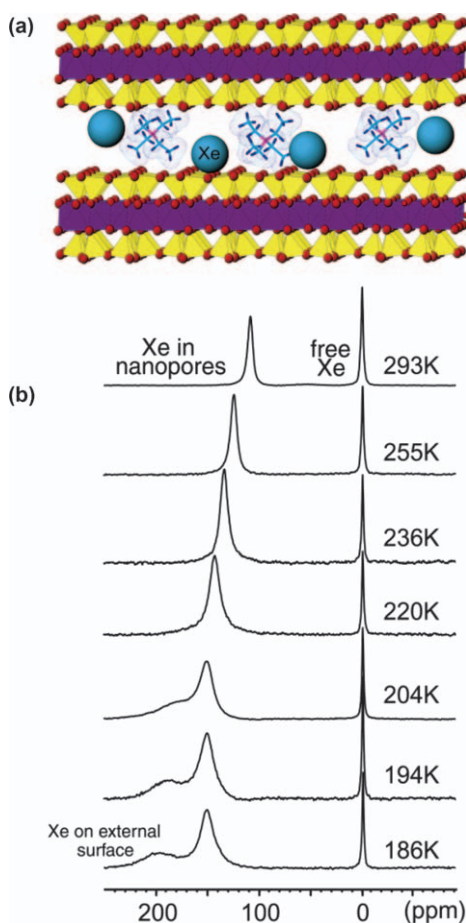


Figure 9.4 (a) Pillared structure of TEA-hectorite: it consists of inorganic pockets of two tetrahedral silicate layers condensed to a central magnesium oxide octahedral layer intercalated by tetraethylammonium cations. (b) CF HP ^{129}Xe NMR spectra of Xe diffusing in the interpillar structure at variable temperature.

adsorption from the vapor phase and by the storage of important gases such as methane and carbon dioxide.

A few further examples of hybrid pillared-clays intercalated by spacers have been recently reported in the literature: in particular, synthetic fluor-ohectorites intercalated with a dication spacer $\text{Me}_2\text{DABCO}^{2+}$ were studied as a function of the layer charge. The HP experiments allowed for a detailed description of the microstructure and it was possible to establish the homogeneity of the pores or, alternatively, a bimodal pore distribution.³⁸ Isothermic heats of adsorption for adsorbate-adsorbent interactions prevailed at low loadings, resulting in an energy of about 25 kJ mol^{-1} , while the isothermic enthalpy of 15 kJ mol^{-1} was measured for competing adsorbate – adsorbate interactions at elevated pressures.

9.4 Metal–Organic Frameworks

Recent years have seen the evolution of a new class of porous materials known collectively as metal–organic framework materials (MOFs) or porous coordination polymers (PCPs).^{14,15} They present diverse open architectures and adsorptive functions, having potential applications in many fields including separation, purification, entrapping of pharmaceuticals and gas storage. Their great diversity and the modularity of the organic moieties make them competitive with zeolites in adsorption, and many potential applications in catalysis can be envisaged. These attractive functions have been based on crystal structure, and in recent years, not only crystallographic studies but also dynamic aspects of framework and adsorption properties have been highlighted because several compounds represent unique guest-responsive frameworks. The storage of gases and vapors, such as methane, hydrogen, acetylene, ethanol, carbon dioxide and benzene, has been achieved, encouraging the application of these frameworks in the field of energy and environment. By HP xenon NMR it has been possible to address the accessibility and the selectivity of the nanochannels as well as the exchange times with the gas phase, elucidating the behavior of adsorption process between gas phase and MOF interfaces.

In the case study presented here, namely aluminum naphthalenedicarboxylate $\text{Al}(\text{OH})(1,4\text{-NDC})$, the crystal structure exhibited a three-dimensional framework composed of infinite chains of corner-sharing octahedral $\text{Al}(\text{OH})_2\text{O}_4$ with 1,4-naphthalenedicarboxylate ligands forming two types of channels with square-shaped cross-section: the large channels present a cross-section of about $8 \times 8 \text{ \AA}^2$, while the small channels are about $3 \times 3 \text{ \AA}^2$ (Figure 9.5). HP ^{129}Xe NMR experiments, in the continuous flow mode, enabled the detection of xenon diffused to the nanochannels, in addition to the gas signal at 0 ppm (Figure 9.5).³⁹ The hyperpolarized ^{129}Xe NMR spectrum of the nanoporous compound, performed at 295 K, revealed a narrow and symmetric signal at $\delta_{\text{Xe}} = 71.8 \text{ ppm}$. The absence of an anisotropic line shape showed that the channels were not narrow enough to impose their anisotropy on to the xenon signal. From theoretical and experimental

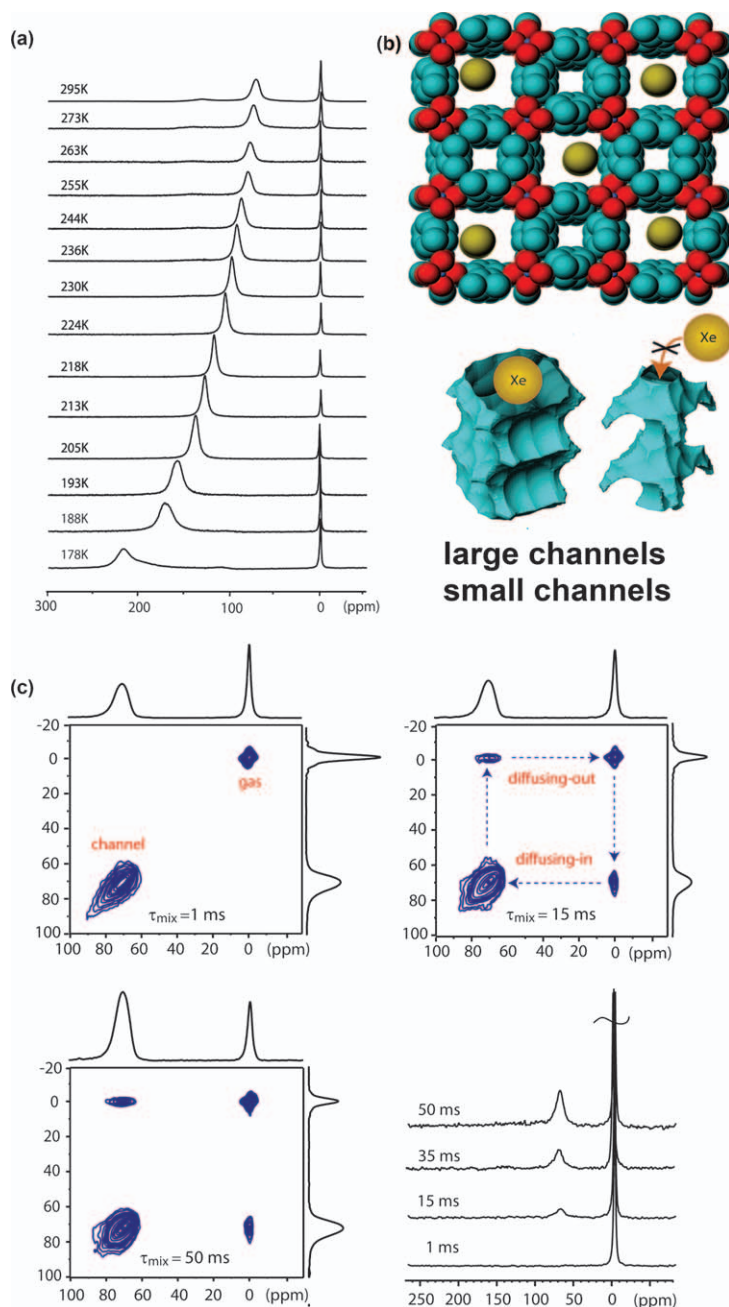


Figure 9.5 (a) CF HP ^{129}Xe NMR spectra at variable temperature: the downfield resonance corresponds to xenon exploring the nanochannels. (b) Crystal structure viewed along the channel axis: the large channels are partially occupied by xenon atoms at low pressure (above). Representation of large ($8 \times 8 \text{ \AA}^2$) and small ($3 \times 3 \text{ \AA}^2$) nanochannels: Xe diffuses selectively in the large nanochannels (below). (c) CF HP 2D exchange ^{129}Xe NMR experiments at distinct mixing times and traces of the 2D exchange spectra at 0 ppm.

studies of ^{129}Xe NMR on zeolites, it could be deduced that a chemical shift value of 72 ppm, under the extreme dilution limit, corresponded to a pore size of about 9 Å, which was consistent with the channels of 8×8 Å², and a diagonal size of 10 Å. The compared evaluation of xenon chemical shifts and XRD analysis were a diagnostic tool to prove that the channels were free from guests and from water molecules in the hygroscopic MOFs. Xenon resonances, collected at a concentration as low as 2%, enabled exclusive observation of xenon–wall interactions, xenon–xenon interactions being prevented. Upon lowering the temperature, there was a downfield shift due to the increased residence time of xenon on the internal surfaces. This behavior was opposite to the observed trend for xenon in narrow-pipes and similar to the middle-size pore zeolites, such as NaY.^{19,40} At temperatures below 205 K, the increase in line width was due to a massive xenon condensation in the channels and the dramatic downfield shift at lower temperatures to the condensation on the external surfaces of the particles. These results demonstrated that the large channels were open and available to be explored by the xenon gas atoms. Indeed, any occlusions or bottlenecks in the framework due to localized collapse of the crystalline structure would hinder effective communication between the cavities and the gas phase. Moreover, at room temperature a low intensity signal at 130 ppm was also detectable in the spectrum, and this is likely due to a minor amount of xenon exploring the small channels. Therefore, small squared channels evaluated by crystallography as about 4 Å diagonal cross-section were hardly accessible to 4.4 Å xenon.

These results show an interesting effect of use of flowing xenon to probe the size of the apertures in complex crystal structures and are particularly effective at low partial pressures (such as 0.02) because no deformation or swelling of the structure is possible. From the fitting of the chemical shift data as a function of temperature, an enthalpy of adsorption was estimated, indicating physisorption phenomena occurred. The value is similar to that of methane which is of a comparable size. The value is twice that found in most molecular organic frameworks, suggesting that xenon is in close contact with more than one surface in the curved channels. From the analysis of the two resonances belonging to the free gas and the xenon exploring the nanochannels at $\delta_s = 71.8$ ppm, the exchange dynamics of xenon between the confined space and the gas phase can be evaluated. In the hyperpolarized ^{129}Xe NMR spectrum at room temperature, the two signals resonate 5460 Hz apart, indicating that the exchange time between the two states, must be longer than 0.2 ms. To evaluate the exchange times on intermediate scales, the experiment of hyperpolarized 2D ^{129}Xe exchange NMR could be employed. The experiment was performed at room temperature, with mixing times ranging from 1 to 50 ms. At 1 ms of exchange time virtually no cross-peaks are present, but starting from a mixing time of 15 ms cross-peaks appear and their intensity increases constantly with the increasing of mixing times. Apparently, the crystals did not present irregularities on the surface or pore obstructions at the channel

ends that would prevent the access to the inner part of the crystals from their surfaces.

The case presented is paradigmatic of the whole class of MOFs, as also highlighted in ZIFs and IRMOFs, which are imidazolate frameworks and iso-reticular metal–organic frameworks, respectively.^{41,42} The chemical shifts at room temperature were moderately moved downfield with respect to the bulk gas, suggesting a limited confinement of the gas atoms in the lattice; consistently, the chemical shift tensors were averaged out and did not show anisotropy. By the application of HP EXSY experiments it was found that the xenon exchanged between the adsorption sites and the free-gas was much slower than that among the adsorption sites within the IRMOF tunnels. The residence time in the crystal was considerably long enough and the pore nanospace large enough to allow for prolonged diffusion of polarized xenon in the galleries. Moreover, metal–organic compounds forming cycles called molecular wheels, and assembled in nanotubes with open apertures, were addressed by 1D and 2D CF HP experiments.^{43,44} The channels did not transfer their intrinsic anisotropy to the xenon lineshape, but diffusion in and out could be singled out by EXSY spectra, exploiting saturation recovery sequences. Intensified signals by interruption of the gas flow were obtained, as independently reported, indicating that the overwhelming amount of freshly hyperpolarized xenon did obscure the local exchange occurring in close proximity to the nanotube apertures.

Shape-persistent conjugated macrocycles self-assembled with *cis*-Pt(II) species, successfully fabricating porous solids. CF HP ¹²⁹Xe NMR was exploited to investigate the solid-state pores of the supramolecular complexes as a function of temperature.⁴⁵ ¹²⁹Xe chemical shifts and temperature-dependent dynamics of Xe atoms in the solids provided useful information on the nature of the pores in these systems. Using the ¹²⁹Xe NMR data, the effective heat of adsorption (ΔH_{ads}) was calculated to be about 29 kJ mol^{−1}.

9.5 Mesoporous Organosilicas

The materials defined as ‘mesoporous’ contain pores much larger than those previously described (>2 nm diameter). Mesoporous materials necessitate directional and robust covalent bonds to sustain such large voids in their architecture. In fact, they are generally constituted by metal oxides and, in most cases, by silica. However, mesoporous silica does not possess any short range crystalline order but only long range periodicity.^{46–49} Regular crystal-like structures can be obtained by using bis-sililated organic building blocks, which can self-assemble in arrays before the formation of the extended network of siloxane bonds. Therefore, these hybrid materials can be grouped under the name of Periodic Mesoporous Organosilicas (PMOs) and can exhibit hexagonal arrangement of the parallel nanochannels with typically 2–4 nm cross-section.^{50,51} Both organic and inorganic groups are exposed alternatively on the internal surfaces of the nanochannels. The use of

organic groups, frequently aromatic rings, entails the possibility of decorating the channel walls with functional groups.⁵² The variety of surface properties and the narrow pore-size distribution made these materials a perfect case to test hyperpolarized xenon as a probe of mesoscale porosity.

The xenon resonance could be collected after a few milliseconds of xenon diffusion in the channels, and down to the limit of low concentration of 2% and low fraction of xenon ($0.02 \text{ mmol Xe g}^{-1}$ organosilica at room temperature).⁵³ Such low concentration guaranteed the exclusive observation of xenon–wall interactions, xenon–xenon interactions being virtually absent. The chemical shift of xenon adsorbed in *p*-phenylenesilica of 4.2 nm channel cross-section was 92 ppm, indicating a typical resonance of xenon exploring a large pore (Figure 9.6). This value was also reported for hybrid materials which contained nanochannels with similar cross-sections of about 4 nm.^{54,55} On decreasing the temperature, there was a downfield shift due to the increased xenon adsorption on the walls, where xenon resided for longer than the residence time in the mesopore space. The dependence of chemical

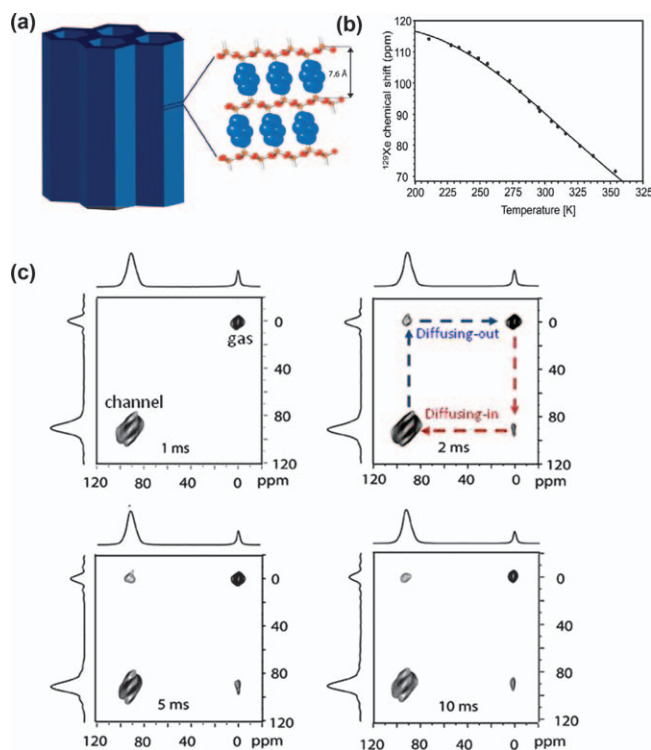


Figure 9.6 (a) Mesoporous *p*-phenylenesilica architecture containing ordered arrays of hybrid building blocks in the channel walls. (b) Chemical shift of xenon diffused into the nanochannels as function of temperature. The chemical shift vs. temperature are fitted by the equation reported in the text. (c) CF HP 2D exchange ^{129}Xe NMR spectra at variable mixing times.

shift on temperature is reported in Figure 9.6. In the approximation of fast exchange and weak adsorption of xenon, the chemical shift was explained by a model of fast exchange between adsorbed xenon on the internal surfaces and xenon diffusing in the free space of the channels. In the space of the pores, xenon experienced the same average interactions as in the gas phase at that partial pressure and, therefore, resonated at 0 ppm, while the chemical shift of xenon on the internal surfaces was not known *a priori*. The dependence of chemical shift on temperature was in agreement with the following equation:

$$\delta = \delta_s \left(1 + \frac{V}{SK_0 R \sqrt{T}} e^{-\Delta H_{\text{ads}} / RT} \right)^{-1}$$

where V and S correspond to the volume and surface area of mesopores, ΔH is the adsorption enthalpy and K_0 is the pre-exponent of Henry's constant.^{53,56} Exploiting the S and V values from nitrogen adsorption (780.34 m² g⁻¹ and 0.78 cm³ g⁻¹, respectively); the nonlinear least-squares fitting of the chemical shift *vs.* temperature gave the values ΔH_{ads} of 13.9 kJ mol⁻¹, δ_s of 119.6 ppm, and K_0 of 1.094×10^{-11} (mol K^{1/2}) (Torr m²)⁻¹. The Henry's constant measured independently by xenon adsorption isotherm was in agreement with the value of K_0 reported above.

The consistency of the parameters from HP ¹²⁹Xe NMR, as well as the nitrogen and xenon adsorption isotherms, indicated that the cylindrical model can be applied to the mesopores, and the absence of hysteresis in the nitrogen adsorption isotherm implies the absence of micropores and defects. Moreover, HP Xe measurements enabled determination of an adsorption ΔH value of 13.9 kJ mol⁻¹, which falls in the range of physisorption. The chemical shift of 119.6 ppm due to xenon probing the surfaces was confirmed by independent measurements on amorphous organosilica with similarly sized channels.⁵⁴ The coverage of the internal surface by aromatic groups was 60%: in fact, larger chemical shifts are observed when silica surfaces are lined with organic moieties.⁵⁷

The exchange dynamics of xenon between the confined space and the gas phase is intriguing: the free gas and xenon exploring the pores resonated at 5600 Hz apart, indicating an exchange time longer than 0.2 ms (this time was determined, in the fast exchange limit, by the formula $\tau \times \Delta\omega \leq 1$, where $\Delta\omega$ is the chemical-shift difference). On the opposite limit, a massive exchange must occur within 200 ms, as a 90° pulse generated an intense signal of hyperpolarized xenon diffused in the pores 200 ms later than the cancellation of the magnetization.²²

To evaluate the exchange times on intermediate scales, the targeted experiment of 2D exchange NMR was employed.^{58,59} At 1 ms of exchange time virtually no cross-peaks were present, while at mixing times longer than 2 ms the intensity of the cross-peaks increased constantly and became substantial, in the order of tens of milliseconds. Consequently, the 2D EXSY experiments straightforwardly demonstrated that the mesopores are open and

accessed easily by the gas flowing within times of a few milliseconds. Interestingly, under continuous flow conditions it was possible to observe separately in the south-east region of the 2D spectrum the exchange peaks of xenon exploring first the free gas and later the limited space of the pores, and in the north-west region xenon diffusing out after a certain confinement time. In the mesoporous materials the intensities of the diffusing-in and diffusing-out exchange peaks were balanced, guaranteeing that the xenon relaxation times are long as compared to the residence times and the reverse pathway from inside to outside the pores occurs when xenon is still intensely hyperpolarized.

Ordered mesoporous silica materials have been extensively used as containers for storing molecules and specifically for controlled drug-delivery. Hyperpolarized ^{129}Xe NMR and magic angle spinning-pulsed field gradient (MAS-PFG) NMR techniques have been used to define the association of mesoporous silicas of the family MCM with the well-known drug ibuprofen.⁶⁰ In these matrices the encapsulated molecules have a mobility compatible with the molecular confinement, and diffusion coefficients are hardly accessible by standard techniques. The multiplicity of signals pointed to the existence of two distinct environments when ibuprofen molecules were included in the host. Therefore, the combined NMR techniques enabled the study of the distribution and the dynamics of ibuprofen encapsulated in porous materials with variable pore diameters.

The heterogeneity of distribution of substances diffused into the mesochannels of MCM-41, such as ammonia borane, was established by Wang *et al.*⁶¹ Indeed, surface domains could be clearly distinguished by variable temperature experiments and, in particular, the bare silica surface and the regions coated by the guest at various filling factors were recognized.

9.6 Polymers with Porous Morphology

Conventional polymers are generally low surface area materials that can absorb xenon by swelling of the amorphous phase, provided the material is observed above its glass transition temperature. However, a proper morphology could considerably increase the surface area and render the material extensively porous and quickly accessible to xenon atoms diffused from the gas phase. Porous morphologies can generally be obtained by quick solvent evaporation or by expansion technologies. Alternatively, the native polymer morphologies were grown forming porous materials thanks to high-yield Ziegler–Natta supported catalysts. A second monomer could reach the catalytic particles percolating through the pores of the polymer already formed and, in turn, polymerize to create an intimate blend. Xenon diffused easily through the porous architecture, collecting data on the phase hierarchy of the material at each stage of the process.⁶²

Notably, the glass transition temperature of each polymer phase could be known from HP xenon experiments even in a complex and intimate blend, contrarily to the DSC analysis. In fact, approaching this critical temperature,

the solubility of xenon in the amorphous phases decreases, implying a progressive signal reduction by lowering temperature. Continuous flow generation of hyperpolarized xenon made this possible because, in the low concentration limit, xenon did not swell the polymer and could only explore the surface-layer of the material within a calibrated time (Figure 9.7).

This new method for determination of the glass transition temperature of polymers is intriguing, although it was realized in polymeric materials with extended surfaces. During the recycle delay, xenon gas rapidly invaded the accessible pores of the millimetre-sized particles because of the open porosity, and then could penetrate the amorphous phase of polymeric materials through the extended surface.

In porous polypropylene (PP) beads the net amount of polarized xenon detected in the polymer particles was reported as a function of temperature. A linear dependence was found on a wide temperature range and a limit temperature of 260 K was extrapolated at zero signal intensity: a clear indication that the material became substantially impermeable to xenon

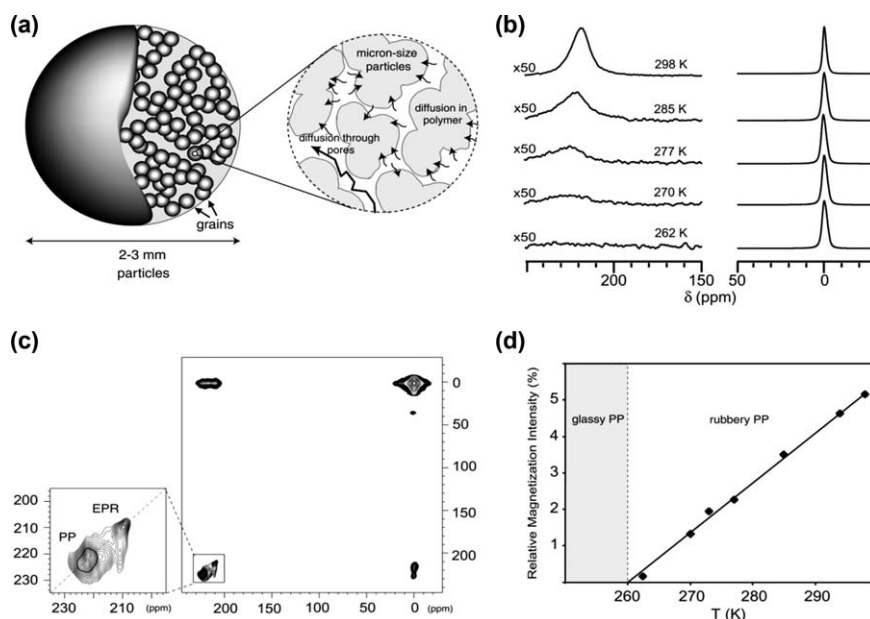


Figure 9.7 (a) Schematic representation of the multigrain morphology of the PP millimeter particle. The grains are about 100–200 μm in size. The diffusion of xenon inside the grains proceeded *via* two pathways: first, rapid diffusion through the pores and second, inside the polymeric amorphous phase of the micrometre-size particles. (b) CF HP ^{129}Xe NMR spectra of Xe gas flowing on PP particles recorded at distinct temperatures. (c) CF HP 2D ^{129}Xe NMR spectrum flowing on a particle made by PP and EPR (57% ethylene) with a mixing time of 500 ms. (d) The ratios of signal intensities of Xe dissolved in PP and the gas phase are reported as a function of temperature.

(Figure 9.7). This temperature corresponds to the glass transition temperature (T_g) of polypropylene, consistent with the fact that the permeability of xenon in the glassy phase is so low as to prevent the recording of a signal, although the high sensitivity of the HP technique enabled xenon diffused into the material to be seen even a few degrees above T_g , when polymer chains experienced slow motional regimes. Therefore, the HP xenon signal was the direct effect of the onset of molecular motion, unlike conventional NMR techniques, which detect fast polymer motions occurring in the MHz regime at far higher temperatures than the glass transition. Quantitatively, under the conditions of high dilution and short diffusion times, the correlation $I \propto (T - T_g)$ was found, where I is the signal intensity normalized on the free-gas signal. This relation mirrors the polymer motional relaxation equation established by the William–Landel–Ferry theory⁶³ and was a strong indication that collective motion of the polymer chains governs xenon diffusion in the bulk material. When two polymers (a homopolymer and a copolymer such as ethylene–propylene rubber – EPR) were polymerized one after the other in the porous beads, they could be singly detected. Since a resonance was present for each polymer phase without coalescence, diffusion was not sufficiently rapid to allow xenon atoms to explore both phases within the NMR experiment time-scale, enabling estimation of the nano-phase dimension. Taking into account 2 ms time for diffusion and the Einstein equation, it was evaluated that the PP and EPR phases had dimensions of about 200 nm. The disappearance of the EPR signals occurred at the extrapolated temperature of 240 K, which is just above the glass transition temperature of 236 K, measured by DSC. The presence of a cross-peak on one side of the diagonal between PP and EPR peaks confirms that, in 500 ms, xenon can enter the EPR phase and then diffuse to the PP one, but the reverse trajectory was shown considerably less probable. The HP 2D exchange spectra of xenon in porous particles constituted by PP and EPR (57% ethylene) provided an example of detailed information collected about xenon flowing among nanophases in a complex phase system.

9.7 Conclusions

The field of porous materials constitutes a vast area of research that is in continuous evolution. HP ^{129}Xe NMR has contributed considerably to understanding shapes and dimensions of the cavities, gas–matrix interactions and, especially, kinetics associated to pore accessibility and to diffusion phenomena. The exchange between cavities or absorptive nanophases as well as between the confined phases and the free-gas, are other unique parameters that can be determined by 2D experiments. In general, the data collected by the diversified HP xenon techniques constitute a rich source of information, complementary to the other available characterization methods of porous materials. Indeed, hyperpolarized xenon NMR reports directly on the voids themselves and the permeable domains of the

material, and allows for the description of complementary features with respect to other spectroscopic techniques.

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CHAPTER 10

Xenon Porometry

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10.1 Introduction

Porous structures can be inorganic, organic and inorganic–organic composite materials. They have many important scientific and technological applications.¹ According to the International Union of Pure and Applied Chemistry (IUPAC), porous materials are classified into three categories: *microporous* materials with pore size less than 2 nm, *mesoporous* materials with pore size between 2 and 50 nm, and *macroporous* materials with pore size larger than 50 nm. Because of the large application range of porous materials it is extremely important that reliable and easy to use methods exist for the determination of their properties.

Properties of porous materials can be studied using a multitude of methods, such as small-angle X-ray and neutron scattering, electron microscopy, gas adsorption, mercury porosimetry, thermometry and NMR spectroscopy.² Xenon porometry is a novel method which makes feasible the determination of mean pore sizes, pore size distribution functions, and porosities.^{3–8} As the name suggests, it is based on applying ¹²⁹Xe NMR spectroscopy. In fact, the method comprises three different ways for determining pore size and one way for determining porosity. The details will be discussed below.

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Interestingly, the first ^{129}Xe and ^{131}Xe NMR experiments⁹ were carried out as early as 1951, only about 6 years after the first successful ^1H NMR experiments. However, a marked increase in the interest to apply ^{129}Xe NMR in materials research occurred only in the early 1980s when it was proposed that it would reveal size information from porous solids.^{10,11} In the course of time it appeared that many disturbing effects contribute to experimental results, and consequently no universal model could be developed to correlate ^{129}Xe chemical shift with pore size. Disturbances arise from xenon–xenon interactions, interaction of xenon with pore walls, and exchange of atoms between the pores and environment. The contribution of xenon–xenon interactions can be diminished by using hyperpolarized xenon-129¹² gas allowing for the decrease of the number of xenon atoms in the pores but yet making experiments feasible in reasonable time. A good example of the correlation of ^{129}Xe chemical shift and mean pore diameter in different porous materials is given in ref. 13.

10.2 The Method

10.2.1 Sample Construction

The sample used in xenon porometry experiments consists of a solid porous material, a medium, and xenon gas, as shown in Figure 10.1.

The xenon porometry method differs from other ^{129}Xe NMR experiments in porous solids in that a proper medium is used. In other words, a medium is introduced into the pores of the material, and xenon gas (either natural or ^{129}Xe enriched) is dissolved in the medium. The medium must possess

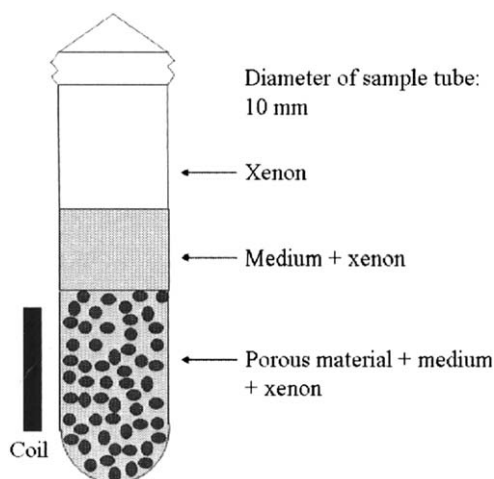


Figure 10.1 Typical sample construction used in xenon porometry experiments. (Reproduced from V.-V. Telkki's PhD Thesis, *Report series in physical sciences*, University of Oulu, Report No. 37, 2006.)

certain properties: (a) it must display a liquid phase in an opportune temperature range so that xenon gas can be dissolved into it, (b) the liquid must be wetting to fill all the pores, and (c) at the phase transition from liquid to solid, the density of the medium should increase properly. The porous solid in turn must contain open pores so that the xenon/medium solution can enter the pores.

10.2.2 Porous Materials

The method has been used to investigate mean pore size, pore size distribution and porosity of various porous solids, but particularly controlled pore glasses (CPG) with the range of mean pore diameter from 81 to 2917 Å. CPG materials (products of Millipore, Billerica, MA, USA) are used in liquid chromatography and related processes. They are incompressible and very durable, and do not shrink or swell in different solutions which are great benefits in testing the workability of the method. Therefore, these materials were chosen to describe the method. Other materials studied include silica gels (Merck, Darmstadt, Germany; mean pore diameter 40, 60 and 100 Å) and Bioran-CPGs (Schott-Geräte BMBH, Hofheim, Germany).

10.2.3 ^{129}Xe NMR Spectra

Figure 10.2 shows an example of ^{129}Xe NMR spectra taken at variable temperatures from a sample consisting of acetonitrile as a medium, xenon gas and controlled pore glass CPG 81. As can be seen, the spectra consist of several resonance lines, contrary to the two lines (one from xenon inside the pores and one from free xenon in between solid particles) detected from a sample in which xenon gas without medium is introduced to the pores.¹⁷ The resonance lines in Figure 10.2 have the following origins:

Signals B and C. In isotropic solutions, ^{129}Xe chemical shift appears typically in the range 150–250 ppm (using the signal from a free xenon gas as a reference), although some exceptions exist.¹⁴ The inset in Figure 10.2 shows two signals at 230 K (at this temperature acetonitrile is in the liquid state) with the chemical shift around 186 ppm. It is obvious that they arise from xenon dissolved in acetonitrile. From a series of experiments at variable temperatures, as shown in Figure 10.2, one can conclude that signal B originates from bulk acetonitrile in between the solid CPG particles; it disappears when bulk acetonitrile freezes. When bulk acetonitrile freezes, signal B disappears, but signal C survives below the freezing point. The spectra in Figure 10.2, however, indicate that the intensity of signal C decreases when moving to lower temperatures. It is known that the melting point of a liquid confined into small pores decreases from that of bulk liquid and the decrease is biggest in the smallest pores.¹⁵ Consequently, from the series of experiments one can draw the conclusion that signal C originates from liquid acetonitrile inside the pores of CPG 81. There exists a

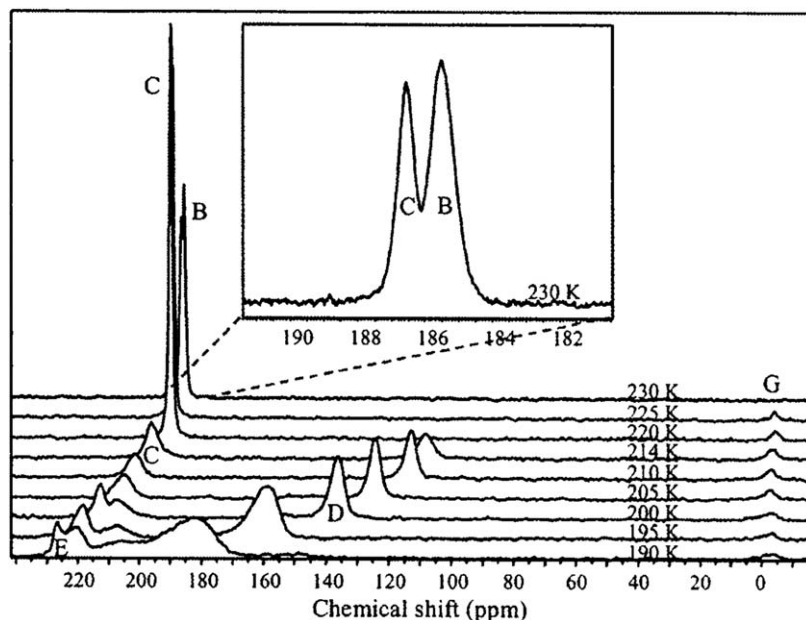


Figure 10.2 ^{129}Xe NMR spectra at various temperatures taken from a sample in which xenon gas is dissolved in acetonitrile and introduced into the controlled pore glass CPG 81. The nominal pore diameter of CPG 81 is 81 Å. Resonance lines labelled with capital letters are identified in the text. The inset shows an expansion of the chemical shift range of signals B and C at 230 K.

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distribution of pore sizes in the material, and freezing proceeds gradually from the largest pores to smallest pores. This leads to a decreasing intensity of signal C, and to a chemical shift distribution within this signal.

Signal D. Figure 10.2 indicates that, with decreasing temperature, a new signal D appears at 214 K. At this temperature, acetonitrile sited inside the largest pores becomes solid. The chemical shift and width of signal D are very sensitive to temperature; when the temperature decreases by about 25 K, the chemical shift increases about 80 ppm. It has been shown that signal D arises from xenon atoms in very small cavities which form inside the pores during the freezing process of the confined acetonitrile.³

Signal E. At the lowest temperature spectrum in Figure 10.2 one can detect another new signal (marked E) with a chemical shift of *ca.* 240 ppm. It arises from liquefied xenon.

Signal G. Near 0 ppm there appears signal G. When bulk acetonitrile freezes, relatively large cavities are formed, and part of the xenon is expelled from the solid acetonitrile into these cavities. The size of cavities is so large that xenon behaves in them as in free space.

10.2.4 Pore Size Distribution Using Solid Medium

As mentioned above, signal D arises from small cavities formed inside the pores during freezing of the used medium. Various media have been used but the present discussion will focus on acetonitrile and naphthalene. Both of them experience a large density increase at the liquid–solid phase transition, as shown in Figure 10.3.

The density of acetonitrile increases about 24% and that of naphthalene about 19% during solidification. There is, however, an essential difference: naphthalene is solid at room temperature but acetonitrile solidifies only at 227 K.

The strong dependence on pore size of the signal D is illustrated in Figure 10.4. Figure 10.4b shows the chemical shift of signal D as a function of mean pore radius, R_p . With increasing R_p , there is a rapid decrease in chemical shift until R_p reaches a value of *ca.* 200 Å. In the R_p range of 200–500 Å an almost flat region appears. From there on, chemical shift decreases monotonically.

The anomaly is a consequence of the density behavior of acetonitrile in the liquid–solid phase transition. This is illustrated in Figure 10.5. In pores with radius larger than a critical radius (200 Å in Figure 10.4), freezing of the medium forms not only cylindrical pockets as shown in Figure 10.5 but also a big enough space in between the pore walls and solidified medium which xenon can enter.

The ^{129}Xe chemical shift of xenon gas inside a small cavity, δ , can be considered the weighted average of δ_S and δ_F , the former stemming from xenon adsorbed on the surface of the cavity and the latter from non-adsorbed (free) xenon in the middle of the cavity:¹⁶

$$\delta = N_S \delta_S + N_F \delta_F \quad (10.1)$$

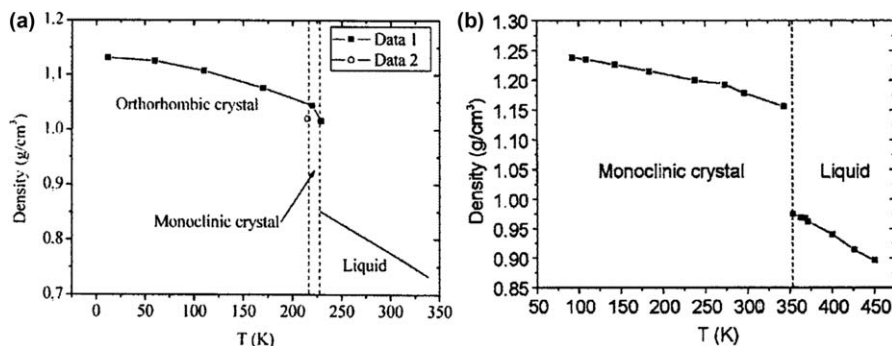


Figure 10.3 Density of (a) acetonitrile (Reprinted with permission from V.-V. Telkki, J. Lounila and J. Jokisaari, *Journal of Physical Chemistry B*, 2005, **109**, 757. Copyright (2005) American Chemical Society.) and (b) naphthalene as a function of temperature. (Reprinted with permission from V.-V. Telkki, J. Lounila and J. Jokisaari, *J. Chem. Phys.*, 2006, **124**, 034711. Copyright (2006), AIP Publishing LLC.)

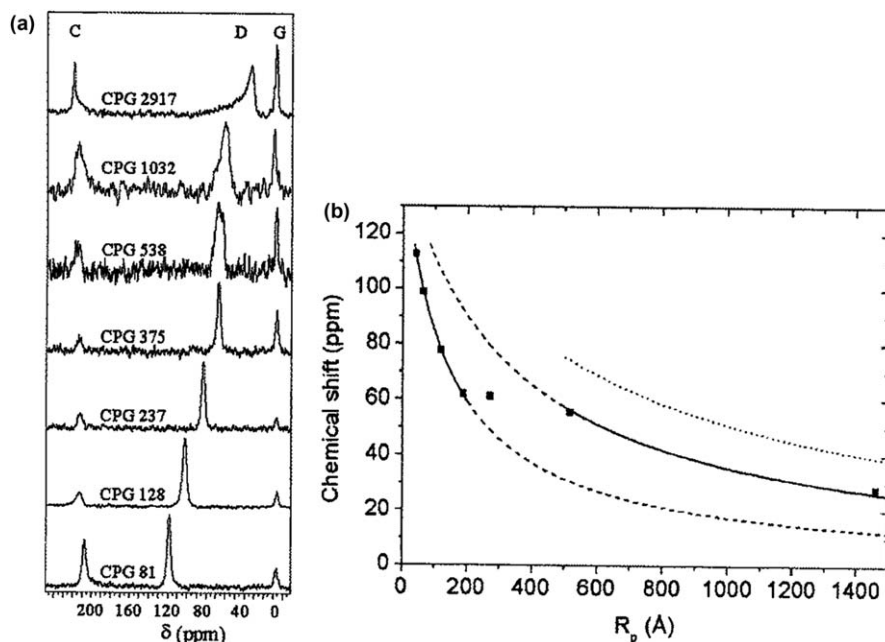


Figure 10.4 (a) ^{129}Xe NMR spectra at 213 K from samples containing CPG X materials, acetonitrile and xenon gas. X refers to the mean pore diameter in Å. The spectra are scaled according to the height of signal D which is the reason for the varying noise level together with the fact that a different number of scans was accumulated. (b) Chemical shift (taken from the spectra on the left) of signal D as a function of mean pore radius.

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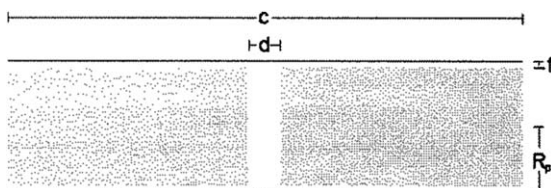


Figure 10.5 Freezing of a medium, such as acetonitrile and naphthalene, in a cylindrical pore of length c and radius R_p . The dark areas indicate solid medium. In pores with smaller than critical radius, the cavity from which signal D arises is a short cylinder (segment of the pore) of length d . In larger pores, also the layer of thickness f between the pore wall and the frozen medium has to be taken into account.

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In this equation,

$$N_i = \frac{n_i}{n_S + n_F}, \quad i = S, F \quad (10.2)$$

is the relative population of the site i , where n_i is the number of moles of xenon in the site i . According to Henry's law, the amount of the adsorbed xenon is, if the gas pressure P is small,

$$n_S = K_H P S \quad (10.3)$$

where K_H is Henry's constant and S is the surface area of the cavity. The amount of free gas can be derived from the ideal gas law

$$n_F = \frac{PV}{RT} \quad (10.4)$$

where V is the volume of the cavity, R is the gas constant, and T is the absolute temperature. If eqn (10.2)–(10.4) are substituted in eqn (10.1) and if the chemical shift of free gas is equal to zero ($\delta_F = 0$), then δ becomes:

$$\delta = \frac{\frac{\delta_S}{V}}{1 + \frac{V}{K_H R T S}} = \frac{\delta_S}{1 + a \frac{V}{S}} \quad (10.5)$$

where $a = 1/(K_H R T)$.

Eqn (10.5) shows that the chemical shift depends of the volume-to-surface ratio V/S , of the cavity. For a cavity of a fixed shape but varying size, V/S is directly proportional to its linear dimension. For example, for a long cylinder of radius R , V/S is equal to $R/2$. Hence, the volume-to-surface ratio of a cavity can in general be written as $V/S = bR$ where R is the relevant linear dimension and b is a coefficient which depends only on the shape of the cavity. Hence, eqn (10.5) can be written

$$\delta = \frac{\delta_S}{1 + abR} \quad (10.6)$$

The inverse of the chemical shift is

$$\frac{1}{\delta} = A + bBR \quad (10.7)$$

where $A = 1/\delta_S$ and $B = a/\delta_S$. In the case of cavities formed during solidification of a medium in pores, the coefficients A and B are cavity-size-independent constants, if the interactions of the xenon atoms with the pore surface and with the solid medium are the same. In that case, a plot of $1/\delta$ versus R should be a straight line, if the shape of the cavity remains constant with increasing size. However, according to the model illustrated in Figure 10.5, the shape does *not* remain constant when the pore size exceeds a critical value. Then the coefficient b decreases abruptly, which means that the slope of the function (10.7) decreases.⁵

The use of a solid medium prevents xenon atoms from moving from one pore to another.⁶ This has been confirmed by using 2D ^{129}Xe EXSY spectra, as shown in Figure 10.6.

The ^{129}Xe EXSY spectra at the top of Figure 10.6 indicate that the shape of signal D is diagonal independently of the length of mixing time. Thus, it can be concluded that diffusion averaging does not contribute to the shape of

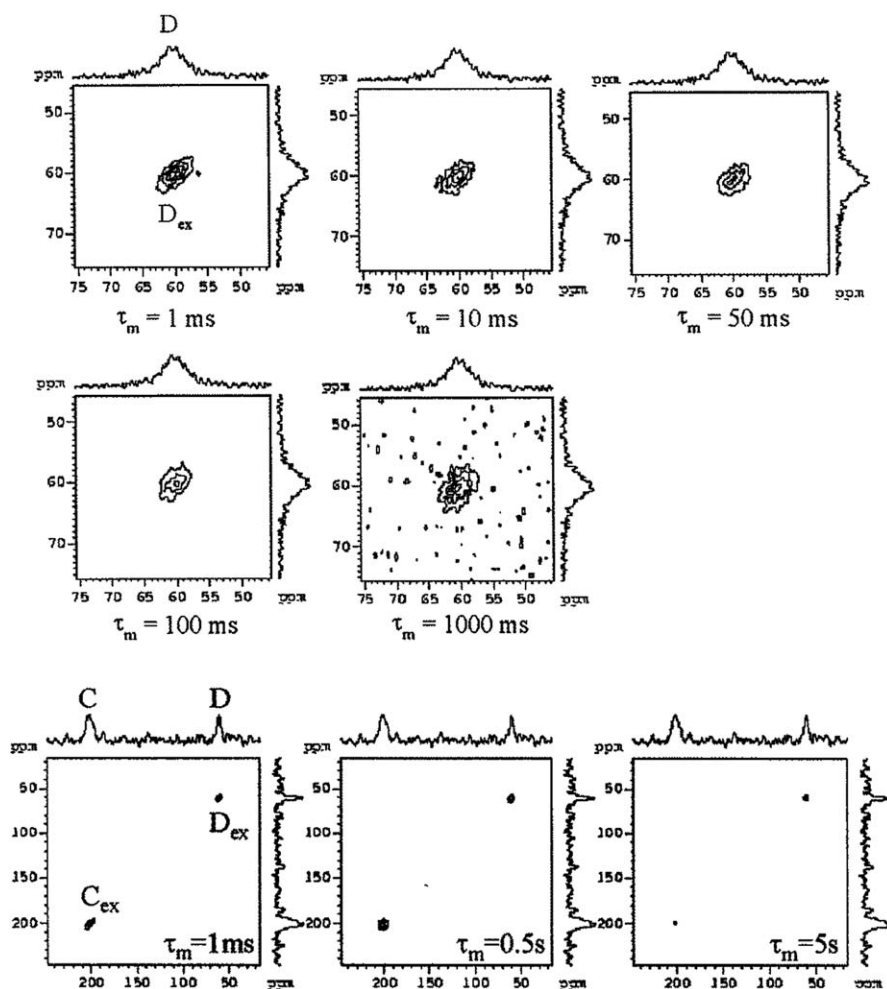


Figure 10.6 (Top) ^{129}Xe EXSY spectra of signal D recorded from a sample containing naphthalene, CPG 81 and xenon. Mixing times are shown below the spectra. (Bottom) ^{129}Xe EXSY spectra of signals C and D taken from the same sample as the spectra on top. Mixing times are shown inside the spectra.

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signal D. The noisy spectrum obtained with a mixing time of 1000 ms is a consequence of the short T_1 (*ca.* 1.8 s) relaxation time. The bottom spectra in Figure 10.6 in turn prove that no exchange between signals C and D takes place.

Consequently, signal D can be considered as a superposition of ^{129}Xe chemical shifts from pores of different sizes. There is a one-to-one correspondence between ^{129}Xe chemical shift and pore size and thus pore size distribution can be determined by simply converting the chemical shift scale to the pore radius scale with the use of an experimentally derived correlation. There is, however, one contribution that may hamper the determination of the pore size distribution. Namely, if R_p is larger than the critical value (200 Å in Figure 10.4), a slow exchange of xenon atoms takes place between the sites d and f (see Figure 10.5), resulting in line broadening. The critical R_p value depends on the medium used. Thus, a medium with smaller density increase at the liquid–solid phase transition will shift the critical radius toward larger values. The whole process of determining pore size distributions from signal D is illustrated in Figure 10.7.

To get an idea about the reliability of the pore size distributions determined by the xenon porometry method, a comparison is made to the data reported by the manufacturer of the CPG materials. For example, xenon porometry results in the full-widths of the distribution functions at the level above which the distribution area is 80% of the total area of 7, 20 and 40 Å for CPG 81, CPG 237 and CPG 538, respectively,⁵ while the corresponding values reported by the manufacturer are 15, 20 and 60 Å.

10.2.5 Pore Size Distribution Using Liquid Medium

Figure 10.2 shows two ^{129}Xe resonance signals, B and C, arising from xenon in liquid acetonitrile, B arising from acetonitrile in between the porous solid particles, and C from acetonitrile inside the pores. The chemical shift difference $\Delta\delta = \delta_C - \delta_B$ appears to depend on pore size, as shown in Figure 10.8.

The relation between the chemical shift difference and the pore radius can be represented by the equation:⁴

$$R_p = c \exp\left(-\frac{\Delta\delta}{d}\right) + f \exp\left(\frac{\Delta\delta}{g}\right), \quad (10.8)$$

where the parameters c , d , f and g get different values in different media and at different temperatures. For example, least-squares fit of function (10.8) to the points measured in acetonitrile at 235 K (see Figure 10.8) results in $c = 144.4$ Å, $d = 0.5453$ ppm, $f = 21.66$ Å and $g = 293.8$ ppm.⁴ The upper limit for available R_p is obtained when signals C and B merge into one, *i.e.* when $\Delta\delta = \delta_C - \delta_B = 0$. In the case of acetonitrile at temperature 235 K, maximum R_p is about 160 Å.

The shape of signal C obviously represents pore size distribution. Therefore, in principle, the determination of pore size and pore size distribution

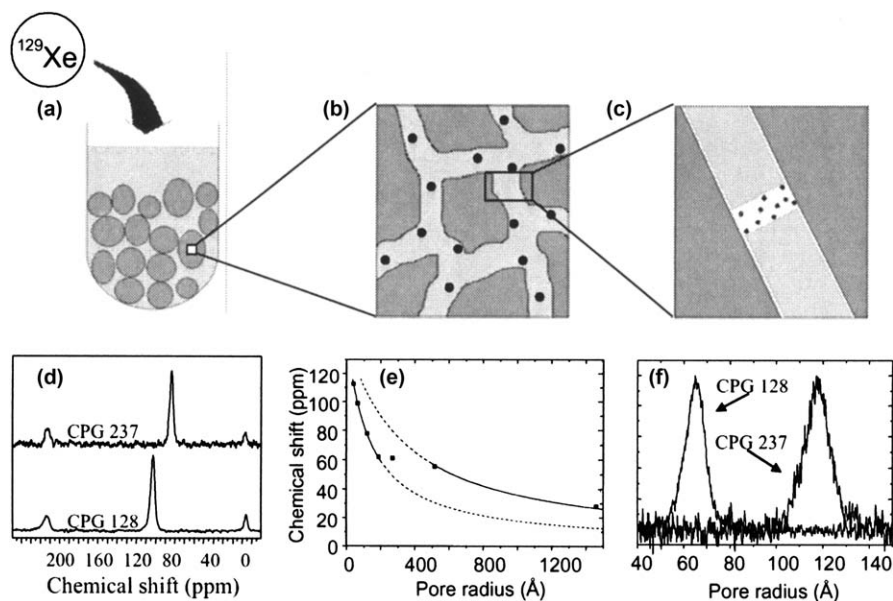


Figure 10.7 Determination of pore size distribution with the aid of signal D. (a) Particles of a porous solid (grey balls) in a medium which in the beginning is in liquid state. Xenon gas is introduced to the liquid. (b) The xenon/medium solution diffuses into the pores and fills them entirely. (c) When the medium solidifies small pockets with xenon expelled from the solid build up. Signal D stems from these pockets. (d) ^{129}Xe NMR spectra are recorded. In the present case, CPG 128 and CPG 237 are used as model compounds. Note that 128 and 237 refer to average pore diameter in Å. (e) Correlation between the ^{129}Xe chemical shift of signal D and pore radius is determined. (f) Pore size distributions are obtained applying the correlation in (e). (Reproduced from V.-V. Telkki's PhD Thesis, *Report series in physical sciences*, University of Oulu, Report No. 37, 2006.)

proceeds in the same way as described above in the case of signal D. In the latter case, however, the use of a solid medium prevents xenon from diffusing between different pores. When using liquid media this may not be the case. To investigate the situation, ^{129}Xe EXSY spectra have been recorded. The results are shown in Figure 10.9.

The shapes of the diagonal peaks C_{ex} and B_{ex} at short mixing times indicate the ^{129}Xe chemical shift distribution: in the space between the CPG particles (the size of which is on average $150\ \mu\text{m}$), from which signal B_{ex} originates, xenon experiences different environments, whereas the shape of signal C_{ex} is evidently due to the pore size distribution. It should be pointed out that the width of signal B_{ex} is also affected by the inhomogeneity of the magnetic field due to the heterogeneity of the sample. Off-diagonal peaks, BC_{ex} , become clearly visible at the mixing time of 30 ms. From Figure 10.9 ($\tau_{\text{m}} = 30\ \text{ms}$) it is evident that the xenon atoms on the surface or near the

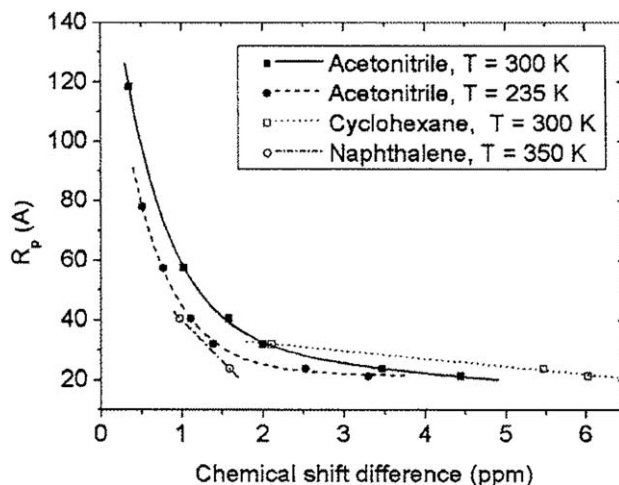


Figure 10.8 Correlation between pore radius and chemical shift difference $\Delta\delta = \delta_C - \delta_B$ in three liquids.

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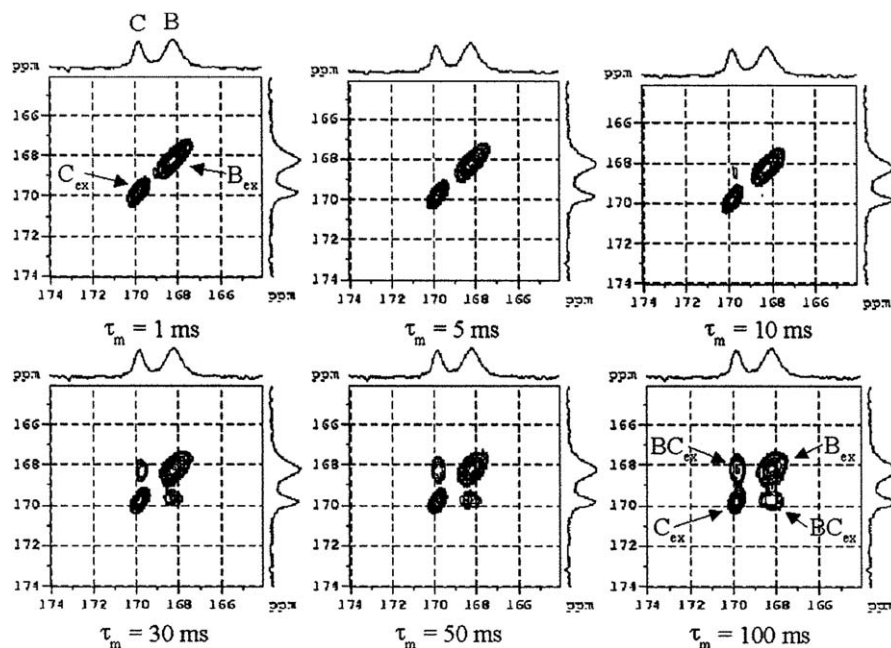


Figure 10.9 ^{129}Xe EXSY NMR spectra from a sample consisting of CPG 81, liquid acetonitrile and xenon. τ_m is a mixing time.

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surface of the CPG particles (and with the largest chemical shift) exchange in a shorter time scale than the atoms further. With growing mixing times signal B_{ex} starts to become round due to the exchange of atoms from different environments in bulk acetonitrile in between the CPG particles. The rounded shape of signal C_{ex} represents an exchange of xenon atoms between the pores of different size.

To find out whether the above described exchange affects the determination of pore sizes one has to inspect the translational diffusion of xenon atoms in a liquid solution during the mixing times, which correspond to observable exchange. Without the value of the diffusion constant, D , of xenon in acetonitrile an estimation has to be based on D values measured in other liquids. For example, in water $D = (2.2 \pm 0.4) \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ and in benzene $(12 \pm 2) \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$,¹⁷ whereas in the isotropic phase of thermotropic liquid crystals D is of the order of 10^{-10} – $10^{-9} \text{ m}^2 \text{ s}^{-1}$.¹⁸ Utilizing D of xenon in water, it can be estimated that the root-mean-square distance that xenon travels during the time period of 30–100 ms is 19–35 μm , the average diameter of the CPG particles being about 150 μm . Thus, xenon atoms in a cavity close to the center of the particle should diffuse a distance of *ca.* 75 μm to reach the bulk liquid site, which is not possible within the given time frame. On the contrary, xenon atoms in cavities close to the surface of the particles may do it.

The diagonal shape of signal C represents the pore size distribution, at least until the mixing time of 30 ms; the smaller the pore the larger the xenon chemical shift. The line width (full width at half height, FWHH) of signal C is approximately 100 Hz, meaning that the NMR time scale of the experiment is *ca.* 1.6 ms which is much shorter than the diffusion time 30 ms, indicating that diffusion does not lead to significant averaging of the resonance signals. Consequently, the shape of signal C makes the determination of pore size distribution fairly feasible. The procedure in the case of signal C (see Figure 10.10) is similar to the one applied to signal D, except that the former is based on a liquid medium and the latter on a solid medium.

10.2.6 Pore Size from Melting Point Depression

Jackson and McKenna¹⁵ have shown, using differential scanning calorimetry, that the melting point depression of liquids confined into pores with diameter of 40–730 Å varies inversely with the mean pore diameter. This means that:

$$\Delta T_{\text{m}} = T_{\text{m}} - T_{\text{m}}(D) = \frac{K}{D} \quad (10.9)$$

where T_{m} is the normal melting point of bulk liquid, $T_{\text{m}}(D)$ is the melting point in pores of diameter D , and K depends on the properties of the substance. The application of NMR spectroscopy to monitor melting of confined substances has led to a method called NMR cryoporometry.¹⁹ In this

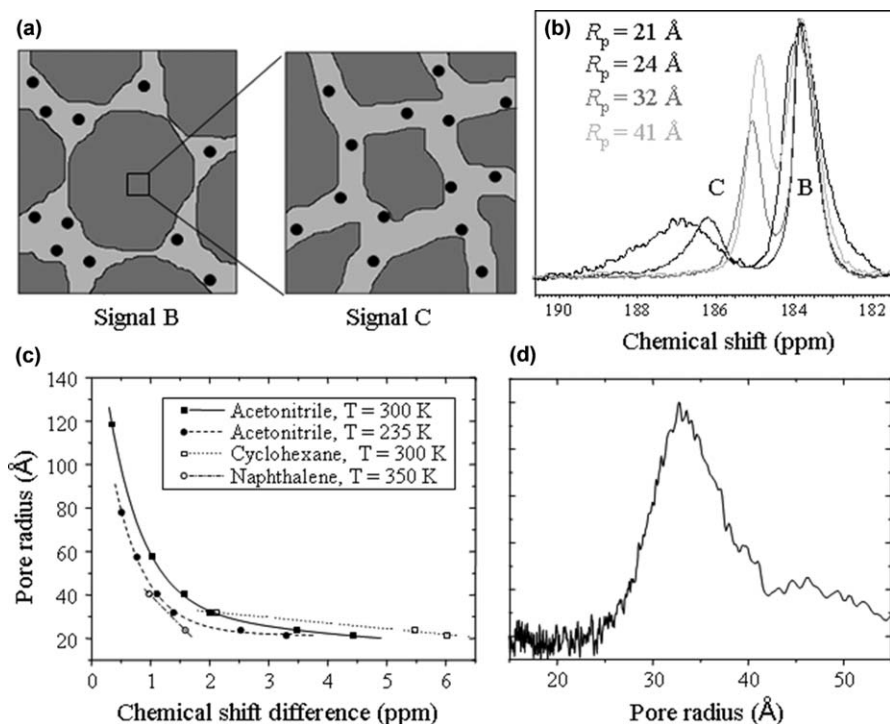


Figure 10.10 Procedure for the derivation of pore size distribution from the shape of signal C. (a) Particles of porous solid material are immersed into a solution of liquid and xenon gas (small black dots). Signal B originates from the space in between solid particles whereas signal C stems from liquid/xenon solution in the pores of the solid particles. (b) For pores of different sizes, signal B remains practically at a fixed chemical shift contrary to signal C whose chemical shift depends on the size of pores. (c) ^{129}Xe chemical shift vs. pore size (radius in the present case) correlation is determined experimentally. (d) Pore size is derived from the shape of signal C using an appropriate correlation, as in (c). (Reproduced from V.-V. Telkki's PhD thesis, *Report series in physical sciences*, University of Oulu, Report No. 37, 2006.)

method, the amount of non-frozen liquid inside the pores is monitored, for example, by proton signal intensity. The liquid state can be separated from the solid state by applying a spin-echo pulse sequence or by using a proper delay after the excitation pulse before the start of FID acquisition. Both methods are based on the much shorter ^1H relaxation times in the solid than in the liquid state.

In principle, xenon porometry offers a similar approach to NMR cryoporometry for determining pore size distributions. As mentioned above and illustrated in Figure 10.2, signal C stems from pores filled with a liquid/xenon gas mixture and its intensity and chemical shift vary with temperature. There are, however, some restrictions which must be taken into account.

For example, the intensity of signal C may experience jumps at phase transition temperatures, *i.e.* when the liquid in pores of certain size solidifies, part of the xenon is expelled to pores filled with liquid. It has been observed that dissolved xenon affects phase transition temperatures shifting them to lower temperature by 0.5–2 K.⁴

10.2.7 Porosity Determination

The porosity (void fraction), ϕ , of a material is a fraction of the volume of void spaces, V_V , from the total volume, V_T , which is a sum of the volumes of the pores, the solid skeleton of the material, and the voids between the particles:

$$\phi = \frac{V_V}{V_T} \quad (10.10)$$

Consequently, ϕ gets values between 0 and 1 (or 0 and 100%). Xenon porometry experiments make feasible the determination of ϕ through the ^{129}Xe integrated intensities of signals B and C which are proportional to the volumes of the voids and pores, respectively. The chemical shift difference of signals B and C should be large enough for reliable integration of peak areas.

10.3 Summary

Xenon porometry affords several methods for the determination of pore sizes and pore size distribution functions as well as porosity. Information about all of them is best obtained by performing a series of ^{129}Xe NMR experiments within a wide temperature range, as shown, for example, in Figure 10.2. Using different media, a fairly large size scale can be covered. The *sine qua non* of the medium, however, is that it possesses both liquid and solid state and its density increases properly at the liquid–solid phase transition. When the medium is in the liquid state, the chemical shift difference of signals B and C provides a means to derive mean pore sizes and pore size distributions. In this case, the maximum available pore size is limited to about 160 Å; however, it is dependent on the used medium and temperature. When the sample temperature is decreased, a phase transition of the medium from liquid to solid state takes place in the pores. Then signal D emerges in the spectra and its position and shape represent the pore size and pore size distribution function. All in all, xenon porometry is a fast and straightforward method to derive diverse information about the properties of porous materials.⁸

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HP Xe-129 NMR Characterization of Single-File Diffusion in Nanotubes

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11.1 Introduction

Single-file diffusion (SFD) is a particular type of diffusion phenomenon occurring in systems of particles confined to one-dimensional channels. In its simplest embodiment, SFD is a manifestation of correlated random displacements in a one-dimensional lattice gas subject to *inter-particle exclusion interaction*. When mutual exchange of positions in the lattice is prohibited, the random-walk (RW) process is inhibited, and like pearls on a string, particles retain their sequential order on the lattice.

SFD has been studied intensively in laboratory channel-particle model systems with *macroscopic* dimensions. The purpose has been to validate theories for the single-file dynamics when the channel properties and particle interactions are well-defined.^{1–6} Significant potential applications to catalysis^{7–10} and separations^{11–19} motivate extension of this work to transport dynamics in *molecular* single-file systems. In functionalized materials with one-dimensional nanochannels, catalytic reaction processes can be strongly impacted by the anomalous transport. For conversion reactions

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

under single-file conditions, traditional mean-field reaction-diffusion equations fail to describe the evolution of concentration profiles, and the scaling behavior of steady-state reactivity is inapplicable.⁷ In molecular separations, mixtures can be more efficiently separated due to the large difference in self-diffusivities of normal and single-file diffusion. For example, in a binary sorbate system composed of large and small molecules satisfying the single-file and normal diffusion criteria within the channels, the self-diffusivity of the smaller molecules can be several orders of magnitude higher. Induction of single-file diffusion by a large molecule on a small molecule in a binary sorbate system can also be envisioned.

One might ask why more research has not been done to characterize diffusion in molecular single-file systems, given its place as one of the key topics of modern transport theory^{20–29} and in view of intriguing potential applications. Only a handful of studies on molecular single-file systems have appeared in the literature, some of which have been controversial.^{30–40} It's a technically challenging problem for two reasons.

Firstly, probing molecular diffusion requires high sensitivity, high dynamic range detection in optically opaque media with high time resolution for tracking molecule displacements over the widest possible time window. These requirements are more stringent for SFD than for normal Fickian diffusion due to the substantially smaller displacements involved. Pulsed field gradient (PFG) NMR is the most common method for measuring self-diffusivities in porous media. The range of displacements that can be probed is a function of the strength of the applied magnetic field gradients, the longitudinal spin relaxation time, and signal-to-noise (generally low due to low thermal polarization and low density). Even in favorable systems (*e.g.* Xe-129), maximum displacements are limited to only a few μm .³⁶ The first reported observation of molecular SFD utilized PFG NMR to measure displacements of CH_4 and CF_4 loaded into several types of zeolites with unidimensional channel structure.^{30,31,37} Inconsistent results on nominally the same materials were attributed to the occurrence of high defect densities and imperfections at the channel openings, allowing mutual particle passages to occur. More recently, PFG-NMR echo attenuation data indicative of SFD of H_2O in single-wall carbon nanotubes was reported,³⁵ but as noted in ref. 38, the measured displacements are too large to be inconsistent with the apparent persistence length of the channels with blocked boundaries. An alternate interpretation of the data in terms of normal diffusion in curvilinear channels has been debated.^{38,39}

Secondly, molecular SFD experiments require highly ideal nanochannel-guest molecule single-file systems. Channels should be monodisperse, at least in the transverse dimensions, and defect free. Many synthetic materials with molecular-scale porosity consisting of one-dimensional channels are known.^{23,31,32,41–46} One-dimensional channel structure has been recently discovered in the crystalline forms of several dipeptides.^{47–53} Evidence for single-file diffusion in several types of molecular crystals has been obtained by hyperpolarized (HP) Xe-129 NMR.^{32–34} In one recent study, HP Xe-129

NMR data acquired using L-alanine–L-valine nanotubes was found to be in essentially perfect compliance with a fully determined SFD model with no fitting parameters.⁴⁰ Occurrence of Xe SFD was confirmed by high gradient PFG-NMR measurements in the same sample.³⁶

Supramolecular chemistry affords new possibilities for synthesizing nanostructured materials suitable for single-file transport studies. The key advantage of this approach is that channel size and shape in the final self-assembled structure is determined by the molecular building-blocks, allowing these properties to be finely tuned for the sorbate(s) of interest.^{54–56} Examples which have been studied by HP Xe-129 NMR include transition metal molecular wheels^{34,57,58} and macrocycles based on the bis-urea motif.^{59–61} This new class of materials is particularly interesting for systematic investigation of one-dimensional transport dynamics.

The use of Xe-129 NMR for characterization of porous media is well documented in the literature, and only the aspects pertinent to single-file nanochannels will be mentioned here. A key property for single-file transport studies is the high sensitivity of the Xe-129 chemical shielding tensor to pore size, shape and orientation.^{62,63} The adsorbed phase signal in sub-nm diameter channels is usually well-resolved from the gas, allowing selective NMR excitation. Xe-129 spin relaxation times in diamagnetic media are notoriously long and can extend into the tens of minutes. In the context of diffusion or chemical exchange studies, a long relaxation time is deleterious to signal averaging but advantageous for measuring long displacements or slow exchange processes. The shortcomings of Xe-129 NMR can be largely overcome by spin exchange optical pumping (SEOP),^{64–66} and with the advent of continuous flow (CF) SEOP,^{67–71} Xe-129 NMR has been extended to a plethora of novel applications in materials science. Not only is the per-scan sensitivity enhanced, continuous flow through the sample holder facilitates faster signal averaging and efficient collection of spectra.

Continuous flow hyperpolarized (CFHP) ¹²⁹Xe 2D-EXSY has been successfully applied to study channel interconnectivities, framework structures, pore geometries, and even combustion reactions⁷² (see Chapters 3.1 and 3.2). It is an elegant approach to the characterization of exchange processes in a pore network. However, caution must be exercised in the extraction of exchange rates in experiments performed with flowing HP gas. Most literature models^{73,74} are valid only for thermally polarized spins in sealed samples. These kinetic expressions, as well as the standard 2D-EXSY pulse sequence, are generally *unsuitable* for CFHP 2D-EXSY. Thus, it is necessary to develop expressions which incorporate flow and relaxation in addition to exchange effects.^{75,76} The same kinetic model forms the basis for HP Tracer Exchange (HPTE) NMR utilizing the selective saturation-recovery pulse sequence.³³ Signal enhancements obtained with ¹²⁹Xe SEOP enable diffusion dynamics to be followed in an observation time window that can span more than 3 orders of magnitude (*ca.* 10 ms–200 s). HPTE NMR, illustrated schematically in Figure 11.1, is a variant of conventional tracer

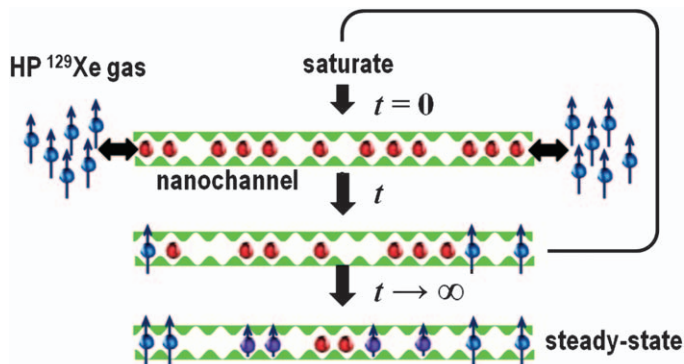


Figure 11.1 Schematic illustration of the HPTE experiment. The NMR spectrum is recorded for a series of repolarization times t following frequency selective RF saturation of the adsorbed phase ^{129}Xe spin polarization.

exchange^{7,8,25,77–83} with the nuclear spin serving as the sorbate tracer label. Utilization of the nuclear spin as a tracer label is advantageous because the system is conveniently re-initialized with chemical shift-selective radio-frequency pulse excitation. While PFG-NMR probes displacements predominantly far from channel openings, HPTE-NMR signals are associated with exchange and diffusion near file openings. The two techniques are thus complementary and when combined yield a more complete picture of the transport dynamics in the system.

11.2 Diffusion Regimes in Single-File Systems

This section reviews some of the elementary concepts of diffusion in systems of particles confined to one-dimensional channels. Aspects relevant to the specific examples presented later in this chapter are emphasized.

11.2.1 Single-File and Center of Mass Diffusion

The fractional occupancy of a channel is defined as

$$\theta = \frac{\# \text{ molecules adsorbed}}{\# \text{ adsorption sites}} \quad (11.1)$$

At low θ , molecules seldom encounter other molecules and Fick's Law is applicable, implying that the mean squared displacement (MSD) $\langle z^2 \rangle$ along the channel axis (z) increases in proportion to time:

$$\langle z^2 \rangle = 2D_0t \quad (11.2)$$

Molecular diffusion in crystals is often a thermally activated process involving hops between adjacent potential energy minima, and in such

cases the self-diffusion constant D_0 can be estimated from the Einstein–Smoluchowski equation:

$$D_0 = \lambda^2 / \tau, \quad (11.3)$$

where λ is the lattice parameter separating potential energy minima and τ is the correlation time for hopping attempts.

When θ is increased (*e.g.* by increasing the partial pressure of the gas), encounters are more frequent, but there's always a short time regime during which free hops occur. It shortens with increasing θ and vanishes in the limit $\theta \rightarrow 1$. With the onset of molecule–molecule encounters, the details of the particle–particle interaction become relevant. For simple exclusion interaction, where occupancy is limited to one molecule per lattice site, mutual exchange of positions in the lattice is prohibited, and the unrestricted RW process breaks down. The MSD time-scaling then enters a second regime – the so-called *single-file diffusion regime*. The single-file criterion for spherically shaped molecules with collision diameter σ_c in smooth, rigid channels with cylindrical symmetry and internal diameter d can be written $d \geq \sigma_c \geq d/2$. For smaller molecules, where $\sigma_c < d/2$, passages can occur and the MSD increases as in normal uni-dimensional diffusion. The two cases are illustrated in Figure 11.2.

The hallmark of SFD is the proportionality of the MSD to the square root of the observation time:^{84–89}

$$\langle z^2 \rangle = 2F(\theta)t^{1/2} \quad (11.4)$$

where

$$F(\theta) = \frac{1-\theta}{\theta} \lambda \sqrt{\frac{D_0}{\pi}} \quad (11.5)$$

To summarize, the analytical model predicts two regimes (not including the ballistic motion at short times) for single-file channel-particle systems: regime I, described by Fickian diffusion (eqn (11.2)) and regime II, described by pure single-file diffusion (eqn (11.4)). Obviously, the transition between

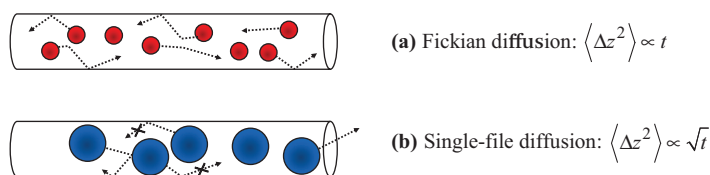


Figure 11.2 The two regimes of diffusion of hard-sphere particles in a cylindrical channel.

diffusion regimes is not abrupt but gradual. A cross-over between the regimes can be defined by

$$\langle \Delta z^2 \rangle_{\text{SFD}}^2 = \langle \Delta z^2 \rangle_{\text{FD}}^2$$

$$\text{Thus, } \tau_{\text{I} \rightarrow \text{II}} = \tau \left(\frac{1 - \theta}{\theta} \right)^2 \quad (11.6)$$

Infinite channels exhibit only these two regimes. In finite-length channels, which are terminated by either blockages or openings to an external phase, a more complex behavior ensues. The MSD in single-file channels blocked at both ends will eventually plateau, entering a *restricted diffusion regime*. In open-ended files, removal of an adsorbed molecule is predicated on removal of all neighboring particles. Particle exchange at both ends of doubly open-ended channels leads to a random walk of the center-of-mass (CM) of the particles in the file that is correlated to individual particle displacements.^{22–25} CM diffusion is characterized by Fickian time-scaling, $\langle \Delta z^2 \rangle = 2D_{\text{cm}}t$, with a reduced diffusivity (in comparison to regime *i*) given by

$$D_{\text{cm}} = D_0(1 - \theta)/(\theta L) \quad (11.7)$$

where D_0 is given in eqn (11.3).^{22,23} While $D_{\text{cm}} \ll D_0$, the $\langle \Delta z^2 \rangle \propto t$ dependence ultimately wins and diffusion enters the *CM diffusion regime* (regime *iii*). For a particle initially located at the midpoint of the channels, the cross-over can be estimated analytically:^{22,23}

$$\langle \Delta z^2 \rangle(t_c) = (2\lambda l/\pi)(1 - \theta)/\theta. \quad (11.8)$$

For other initial distributions, deviations from the $t^{1/2}$ time-scaling of the MSD occur at shorter diffusion times, depending on proximity to the file boundary and boundary conditions.

Singly-open ended channels do not support CM diffusion: diffusion in such channels enters a restricted regime.

11.2.2 Tracer Exchange

Exchange dynamics in open ended channels can be accessed by the so-called *tracer exchange* methodology. Tracer exchange monitors the uptake of labeled molecules by a porous material which is initially saturated with unlabelled molecules (or *vice versa*). The tracer exchange curve is defined as

$$\gamma(t) \equiv \frac{n_{\text{ads}}(t)}{n_{\text{ads}}(\infty)} \quad (11.9)$$

where $n_{\text{ads}}(t)$ is the number of labeled molecules adsorbed at time t . A conventional tracer label might be isotopic or fluorescent. For tracer

exchange at short t in one-dimensional channel-particle systems where exchange is diffusion limited, the RW model yields²⁵

$$\gamma(t) = \frac{1}{l} \sqrt{\frac{8}{\pi} \langle z^2(t) \rangle} \quad (11.10)$$

$$= \frac{4}{l} \sqrt{\frac{F}{\pi}} t^{1/4} \text{ (SFD)} \quad (11.11)$$

11.3 Kinetic Monte Carlo Simulation

Kinetic Monte Carlo (KMC) simulations are a useful tool for exploration of diffusion dynamics within the scope of the RW model. KMC simulations are computationally limited to relatively short channels or short time-scales (MD simulations are even more limited). Nevertheless, KMC simulations provide insight into the effects of varying initial particle distribution, file boundary effects, file lengths, particle occupancy, and transport impedances (*e.g.* desorption barriers, blockages, defects...) on diffusion dynamics, as observed in tracer exchange or PFG-NMR experiments.

In simulations pertinent to PFG-NMR, channels are initialized with a tagged particle at the midpoint. For each simulation (time) step, particles make hop attempts to the left or right, and the particle is moved from its current site to the adjacent one only if that site is unoccupied. Unlike real diffusion, particle hops in a computer simulation are executed in series, so it is crucial to shuffle the hopping sequence to avoid systematic errors. Fast exchange at file openings is simulated at each time-step by populating the boundary site with an untagged particle with a probability equal to the fractional loading. This procedure ensures time-invariance of the loading. Simulations in doubly open-ended channels (Figure 11.3a) exhibit the cross-over from ND to SFD and SFD to CM diffusion, in accordance with eqn (11.6) and (11.8), respectively. Simulations in singly open-ended channels illustrate that *CM diffusion is completely suppressed* in such channels. Instead, the simulations confirm a cross-over to restricted diffusion.

In tracer exchange simulations, channel sites are initialized with unlabeled particles with a probability θ . Tagged particles in the reservoir enter the file boundary site with the same probability. Particles within the file make hop attempts to the left or right in a sequence that is shuffled prior to each time step. At each sampling interval, the tracer exchange signal is calculated by summing the number of tagged particles in all channels.

A representative KMC simulation of tracer exchange on a double log scale, together with a fit to the function $\log \gamma \propto a \log t$, is shown in Figure 11.3b. The following conclusions are drawn from the simulations:

- (i) Fitting of the KMC yields a time exponent $a = 0.27$, in good agreement with the RW model ($a = 0.25$).

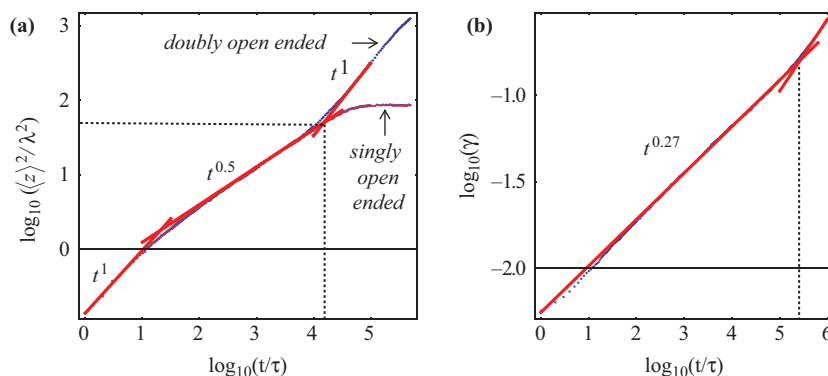


Figure 11.3 (a) KMC simulation of the MSD of tagged particles as a function of the simulation time steps with free exchange at the file boundaries. The ensemble of 10 000 single-file channels, each consisting of 201 lattice sites, was initialized with tagged particles in the middle sites. Remaining sites are randomly populated with untagged particles with $\theta = 0.7$. The cross-over from SFD to CM diffusion can be seen after $10^{4.2}$ time steps, consistent with eqn (11.8), for channels with open boundaries. Singly-open ended channels exhibit a transition to restricted diffusion. (b) Simulation of standard tracer exchange curve. The increase in slope from 0.27 to 0.42 marks the apparent transition to CM diffusion. The cross-over time is shifted by a factor of 20 in the number of simulation time steps in comparison to the cross-over in MSD observed when the tag is initially placed in the middle of the channels.

- (ii) Eqn (11.8) is valid only when tagged particles originate in the middle of the file. It does not apply to the tracer exchange initial condition in which labeled particle originate in the reservoir.
- (iii) CM diffusion is fully suppressed in singly open-ended channels, irrespective of the initial condition.

11.3.1 Spin Exchange Optical Pumping

HP Xe-129 for NMR studies can be produced by SEOP, as illustrated in Figure 11.4.^{64,65} High capacity, continuous flow production of HP Xe-129 is achieved using high power semiconductor laser diode arrays (LDAs).^{66,70,90,91} Nowadays, polarization levels exceeding 70% are obtained.⁹¹ Helium or nitrogen is typically added to attain efficient optical absorption. However, for fundamental studies it is preferable to use pure Xe, despite the resulting lower polarization level.

A block diagram of the SEOP setup at the University of Florida is shown in Figure 11.5. The sample holder consists of a 3 mm (O.D.) cylindrical sample holder machined from PEEK. Details are provided in ref. 70.

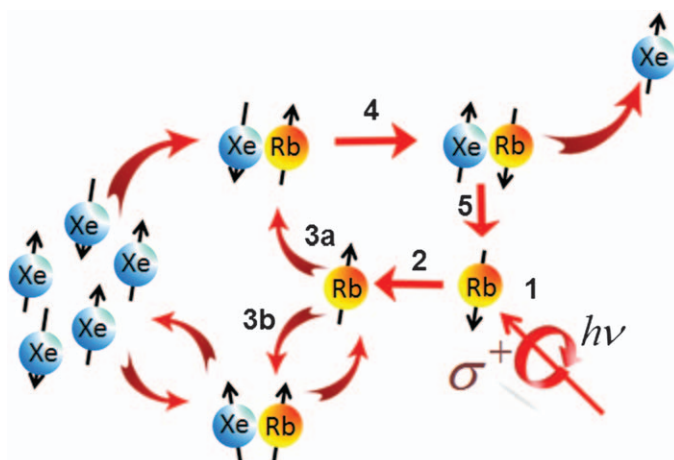


Figure 11.4 The Rb–Xe- ^{129} spin exchange optical pumping cycle. Step 1: Rb absorbs 794.5 nm σ^+ photon. Step 2: Rb is optically pumped. Step 3a. Rb collides with Xe in spin-down state. Step 3b. Rb–Xe collision in spin up state – unproductive; Step 4: spin exchange mediated by hyperfine interaction. Step 5. Polarized Xe accumulates, exiting pumping cell. Rb in spin down state enters next iteration of cycle.

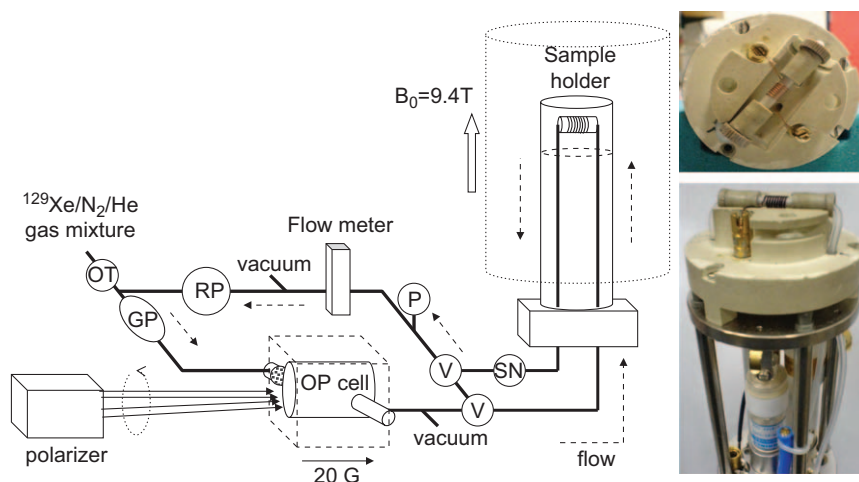


Figure 11.5 Experimental layout for continuous flow Xe- ^{129} spin exchange optical pumping NMR.⁷⁰ Flow is interrupted by actuating a solenoid valve (SN) at the outlet of the sample holder. Two three-way valves (V) allow isolation of the optical pumping system from the sample holder. (P: pressure gauge, OT: O_2 trap, GP: gas purifier, RP: re-circulation pump.) Top and side views of a modified Bruker wide-line probe head showing peak sample holder, RF coil, PEEK tubing connectors on inlet and outlet, and PFA tubing.

11.4 Xenon-129 NMR in Single-File Channels

The Xe-129 chemical shielding of Xe confined to one-dimensional pores depends sensitively on the channel morphology, chemical composition of the channel structure, channel orientation with respect to the static magnetic field, and Xe loading. A comprehensive treatment on the effects of confinement in one-dimensional channels on the Xe-129 NMR chemical shift is provided by Jameson *et al.*⁶² The single-file nature of Xe has been demonstrated in a wide variety of porous media having long one-dimensional channels. Examples include Dianin's compound,⁴¹ TPP,^{32,42} dipeptides (L-alanyl-L-valine, L-valyl-L-alanine),^{33,36,40,48,52,53,63} molecular sieves⁸¹ (AlPO-11, AlPO-5, SSZ-24), and transition metal molecular wheels.³⁴

The Xe loading dependence of the Xe-129 shielding tensor is a key indicator of single-file loading. At high loading, the Xe-Xe interactions give rise to large paramagnetic contributions to the $\sigma_{\perp}$ component but not the $\sigma_{\parallel}$. The predicted shielding tensor resulting from Xe in cylindrical *narrow bore pipe* channels is predicted to be axially symmetric. Defining

$$\sigma_{\parallel} = \sigma_{zz}$$

$$\sigma_{\perp} = \sigma_{xx} = \sigma_{yy}$$

where σ_{xx} , σ_{yy} , and σ_{zz} are the principal values of the shielding tensor. The *shielding anisotropy* is given by

$$\begin{aligned}\xi &= \sigma_{zz} - \frac{1}{2}(\sigma_{yy} + \sigma_{xx}) \\ &= \sigma_{\parallel} - \sigma_{\perp}\end{aligned}$$

The Xe-129 powder pattern exhibits a systematic variation with Xe density due to the effect of Xe-Xe interactions,⁶² as illustrated in Figure 11.6. At the loading where Xe-Xe interactions and Xe-wall interactions are balanced, $\sigma_{\perp} = \sigma_{\parallel}$ and an isotropic line shape may be observed (see Figure 11.7).

11.4.1 CFHP Xe-129 NMR in AV

As noted above, some dipeptides are known to form crystal structures with one-dimensional channels. Ones that have been studied by CFHP Xe-129 NMR include L-alanyl-L-valine (AV) and its retro-analog L-valyl-L-alanine (AV).^{33,34,49,50,65} In the hexagonal crystals (P6₁ space group)^{53,63} of AV and VA, helical channels are formed by hydrogen bonded assembly. The winding spacing in AV and VA is nearly the same (*ca.* $c = 10$ Å). The radius of the channel center from the 6₁ axis is 0.60 and 1.05 Å, respectively.^{53,63} The Xe atom, with a diameter $\sigma_{\text{Xe}} = 0.44$ nm, satisfies the single-file criterion in AV and VA, where the mean channel diameters are 0.51 and 0.49 nm, respectively.^{53,63} The single-file nature of Xe in AV is evidenced by the loading

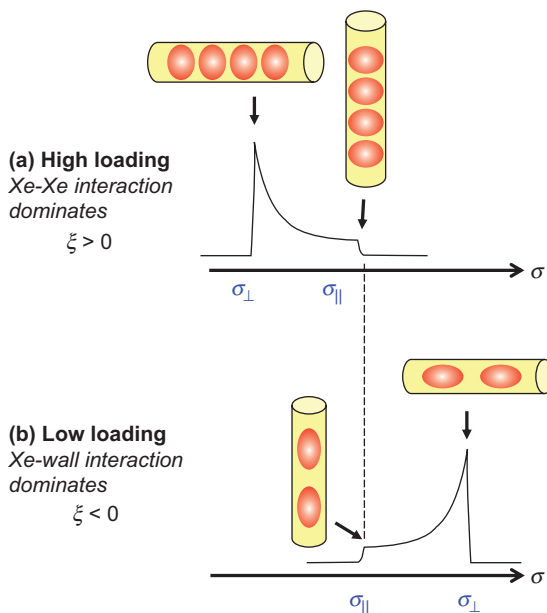


Figure 11.6 Expected shielding components for Xe-129 at (a) high loading and (b) low loading in a circular narrow-bore pipe. $\sigma_{\parallel}$ is the component along the axis of the pipe.

dependence of the ^{129}Xe chemical shift tensors.⁶³ The temperature dependence of the Xe loading is apparent in Figure 11.7.³³

An empirical correlation between chemical shielding and loading can be obtained from adsorption isotherm data. Once established, the correlation can be used to infer channel occupancy in CFHP NMR experiments.^{33,53} Shielding tensor components are extracted from fits to the powder pattern line shapes. AV exhibits a Langmuir adsorption isotherm.⁵³ At room temperature, the correlation between loading and shielding component $\sigma_{\perp}$ is approximately linear over a wide range:³³

$$\theta_m = 0.0054 \cdot \sigma_{\perp} - 0.52 \quad (20^\circ\text{C}) \quad (11.12)$$

Molar loading θ_m is converted to volumetric fractional occupancy (θ) based on the crystal structure.

11.4.2 Hyperpolarized Xenon-129 NMR of Flowing Gas

In a flowing gas, nuclear spin magnetization is replenished due to the residence time in the NMR detection coil. Given a flow rate f and a detected volume V , a residence time $\tau_R = V/f$ can be estimated. Replenishment of magnetization following NMR saturation obeys

$$\frac{dM_g}{dt} = \frac{M_i - M_g}{\tau_R} \quad (11.13)$$

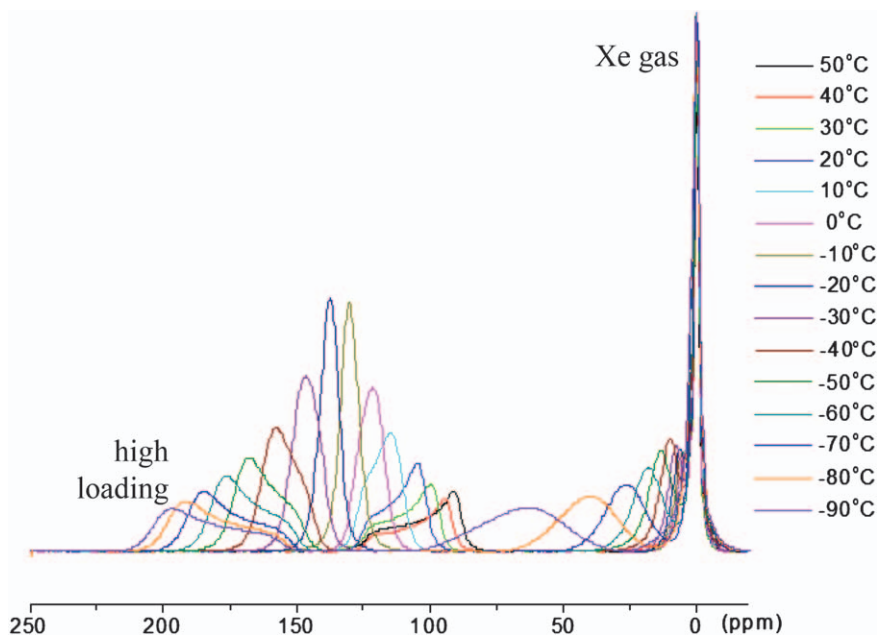


Figure 11.7 Steady-state CFHP ^{129}Xe NMR spectra of Xe adsorbed into polycrystalline AV at a Xe partial pressure of 3300 mbar (4600 mbar total pressure) at a series of temperatures, as indicated. Chemical shifts are referenced to the gas phase peak.

11.4.3 Surface Exchange Kinetics

Rate equations describing magnetization exchange between a flowing gas and a surface adsorbed phase are developed in this section. Although Langmuir adsorption is assumed, the same approach could be extended to other types of adsorption. The Langmuir surface consists of N thermodynamically equivalent adsorption sites. The $n_c = N\theta$ adsorbed molecules are in dynamic equilibrium with n_g gas molecules, as depicted in Figure 11.8.

The kinetic rate of change in coverage due to adsorption is proportional to both the number of unoccupied sites available and the amount of gaseous sorbate:

$$\frac{d\theta}{dt} = k_a n_g N(1 - \theta) \quad (11.14)$$

For desorption,

$$\frac{d\theta}{dt} = -k_d N\theta, \quad (11.15)$$

k_a and k_d are rate constants for adsorption and desorption, respectively. Since in the steady-state, $d\theta/dt = 0$, the adsorption and desorption rates are related:

$$k_d = k_a n_g \left[\frac{1 - \theta}{\theta} \right] \quad (11.16)$$

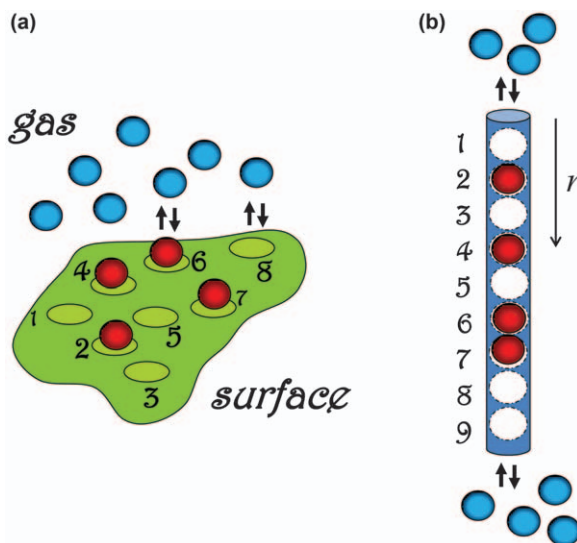


Figure 11.8 Langmuir adsorption (a) on 2D surface (b) in a 1D nanotube topology.

Using eqn (11.14)–(11.16), the rate equation for the surface magnetization is formulated, with longitudinal spin relaxation included:

$$\frac{dM_c}{dt} = k_a n_g N(1 - \theta) I_{zg} - k_d N \theta I_{zc} - \frac{N \theta I_{zc}}{T_{1s}} \quad (11.17)$$

$$= k_d N \theta I_{zg} - k_d N \theta I_{zc} - \frac{N \theta I_{zc}}{T_{1c}} \quad (11.18)$$

$$= k_d \frac{N \theta}{n_g} M_g - k_d M_c - \frac{M_c}{T_{1c}} \quad (11.19)$$

In the gas phase,

$$\frac{dM_g}{dt} = -k_d \frac{N \theta}{n_g} M_g + k_d M_c - \frac{M_g}{T_{1g}} + \frac{M_i - M_g}{\tau_R} \quad (11.20)$$

11.4.4 Langmuir Adsorption in Single-File Nanotubes

Eqn (11.19) and (11.20) pertain to a homogeneous surface with N adsorption sites that are both thermodynamically and kinetically identical. Similarly, the N adsorption sites in an ensemble of single-file nanochannels are also thermodynamically equivalent (neglecting end-effects), and may exhibit a Langmuir adsorption isotherm. An important difference, however, is that

the adsorption sites in a single-file channel are not all equally accessible to the external surroundings. Exchange is predicated on diffusion to the opening. Diffusion limited exchange kinetics in channels can be modeled by replacing the single value of the rate by one that depends on displacement from the channel opening.

$$k_{dl} = \tau_l^{-1} = \begin{cases} 4F^2 / z^4 & SFD \\ 2D / z^2 & ND \end{cases} \quad (11.21)$$

$$(11.22)$$

11.4.5 CFHP Xe-129 2D-EXSY

Xe-129 2D EXSY has been employed extensively to investigate slow exchange of Xe in diverse materials, including liquid crystals,^{92,93} zeolites,^{73,94,95} polymers,^{78,96,97} and carbon nanotubes.^{98,99} The appearance of the spectrum immediately provides information about the interconnectivities in pore space networks.^{69,71,100–102} Exchange is manifested as cross-peaks in the 2D-EXSY spectrum. Rates of exchange are extracted from the mixing time dependences of the diagonal-peak and cross-peak signals and least-squares fitting to an appropriate kinetic model. Quantitative analysis of ¹²⁹Xe 2D-EXSY have been limited mostly to thermally polarized conditions,^{73,92,94,103} for which multi-site exchange models have been established.^{74,94,104} An elegant example is provided by Tallavaara *et al.* in the extraction of the exchange rate and T_1 in a liquid-crystal phase confined in controlled-pore glass.⁹² It is a rather heroic accomplishment from a technical perspective. Thermally polarized ¹²⁹Xe experiments typically suffer from inherently low sensitivity or unacceptably long acquisition times for mixing-time dependence experiments, ranging from hours to days per 2D spectrum. While rate constants and spin relaxation times can be determined from a 2D-EXSY spectrum acquired at a single mixing time,^{73,74,94} thereby minimizing the total experiment time, the accuracy is generally lower than that which can be achieved by acquiring multiple 2D-EXSY spectra at a series of mixing times.^{73,74,92,104}

For CFHP Xe-129, the standard 2D-EXSY sequence is pre-pended with a saturating RF pulse train (SAT) followed by a fixed re-polarization delay τ_1 , as shown in Figure 11.9.⁷⁵

With the continuous flow of HP gas through the sample, steady-state adsorption is obtained. Non-selective saturation yields $M_g(0) = M_s(0) = 0$. The solution of eqn (11.19) and (11.20) for $M_g(\tau_R)$ and $M_s(\tau_R)$ is simplified under the following conditions: (i) if $\tau_R \ll T_{1g}, T_{1s}$, relaxation terms can be safely neglected; (ii) when $N\theta/n_g \ll 1$ (*i.e.* when gaseous Xe atoms are present in large excess), re-polarization of the gas is dominated by the influx of HP gas into the sample space.

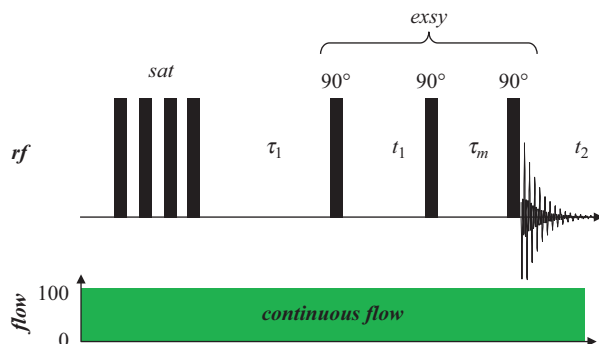


Figure 11.9 CFHP 2D-EXSY pulse sequence.⁷⁵ τ_m is the mixing time. An 8 step phase-cycle is employed for coherence transfer pathway selection.

The magnetizations in the gas and channels at the beginning of the mixing delay are

$$M_g^\circ \equiv M_g(\tau_1) \approx M_i \left(1 - e^{-\tau_1/\tau_R} \right), \quad (11.23)$$

$$M_c^\circ \equiv M_c(\tau_1) \approx M_i \left[\frac{N\theta}{n_g} \right] \frac{(1 - e^{-k_d\tau_1})\tau_R^{-1} - (1 - e^{-\tau_1/\tau_R})k_d}{\tau_R^{-1} - k_d}. \quad (11.24)$$

Longitudinal magnetizations that do not exchange during τ_m yield *diagonal* peaks, which decay mono-exponentially:

$$M_{g \rightarrow g}(\tau_1, \tau_m) = M_g^\circ \exp \left[-\tau_m \left(\frac{1}{\tau_R} + k_d \frac{N\theta}{n_g} \right) \right] \quad (11.25)$$

$$M_{c \rightarrow c}(\tau_1, \tau_m) = M_c^\circ e^{-k_d\tau_m} \quad (11.26)$$

Cross-peaks signals representing molecules adsorbing and desorbing during the mixing time (gas atoms in excess) are

$$M_{g \rightarrow c}(\tau_1, \tau_m) = M_g^\circ \frac{k_d}{\tau_R^{-1} - k_d} \frac{N\theta}{n_g} \left(e^{-k_d\tau_m} - e^{-\tau_m/\tau_R} \right) \quad (11.27)$$

$$M_{c \rightarrow g}(\tau_1, \tau_m) = M_c^\circ \frac{k_d}{\tau_R^{-1} - k_d} \left(e^{-k_d\tau_m} - e^{-\tau_m/\tau_R} \right) \quad (11.28)$$

The functional forms given by eqn (11.27) and (11.28) reveal the following:
(i) cross-peaks for adsorption and desorption generally have unequal amplitudes, but otherwise have the same time-dependence, maximizing at

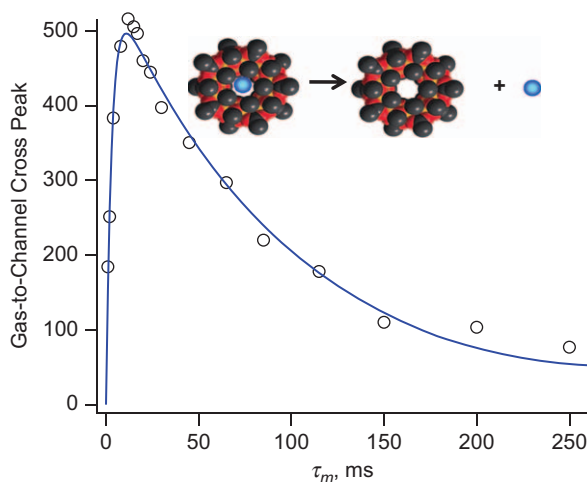


Figure 11.10 Gas-to-channel cross-peak signal as a function of the mixing time. Each data point (open circles) represents a complete 2D-EXSY experiment. Solid blue curve is the best fit of eqn (11.28) to the cross-peak signal integral data.

$\tau_m^* = \ln(k_d \tau_R) / (k_d - \tau_R^{-1})$; (ii) cross-peaks vanish in the limit $\tau_R \rightarrow 0$ or $k_d \rightarrow 0$; (iii) cross-peaks are significantly affected by flow when $\tau_R^{-1} > k_d$; (iv) the slope of $\log(M_g \rightarrow c)$ or $\log(M_c \rightarrow g)$ vs. τ_m for short mixing times $\tau_m \ll \tau_R$ yields the desorption rate, k_d .

As an example, the experimental mixing time dependence of the desorption cross-peak obtained in Ga₁₀ wheel nanotubes is shown in Figure 11.10.

11.4.6 Interrupted Flow Hyperpolarized 2D EXSY

By inspection of eqn (11.27) and (11.28) it is clear that very high flow rates, where $\tau_R \rightarrow 0$, yield vanishing cross-peaks, while as τ_R increases, cross-peaks increase, maximizing at longer τ_m . Unfortunately, reducing the flow rate is not favorable for retaining high polarization due to relaxation losses during transport from the polarization cell to the sample.

The solution demonstrated in ref. 76 is interrupted flow hyperpolarized (IFHP) EXSY, as shown in Figure 11.11, which can be implemented by inserting a solenoid valve. An auxiliary TTL gate on the spectrometer is used to synchronize actuation of the solenoid valve with the rf excitation. Figure 11.12 compares the gas peak signal integrals acquired with the EXSY pulse sequence with a fixed evolution time t_1 in IFHP and CFHP modes. The gas peak observed using IFHP mode decays much more slowly as a function of mixing time.

The HP ¹²⁹Xe 2D-EXSY spectra of Xe in AV nanotubes acquired at two different mixing times are presented in Figure 11.13. Features worth noting are: (i) cross-peak integrals for the gas $\rightarrow$ channel and channel $\rightarrow$ gas

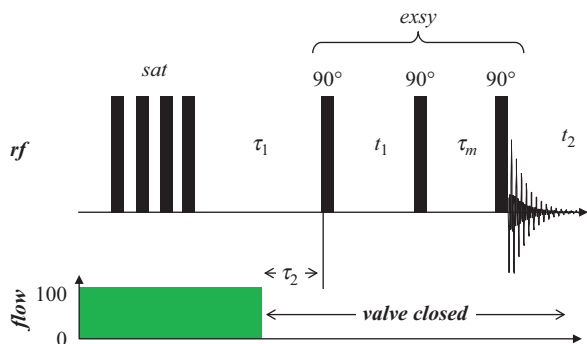


Figure 11.11 Pulse sequence timing diagram for interrupted flow HP 2D-EXSY. The solenoid valve stops the flow near the end of the re-polarization delay. The system is allowed to settle for $\tau_2 = 1$ s prior to application of the standard EXSY pulse sequence.

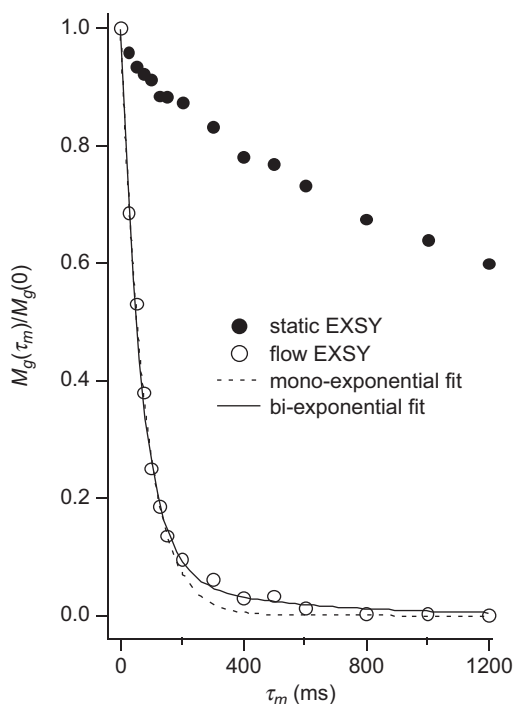


Figure 11.12 Plot of gas phase Xe-129 signals acquired as a function of mixing time τ_m in IFHP (static) and CFHP (flow) EXSY modes at a flow rate of 100 mL min^{-1} using a fixed evolution time $t_1 = 100 \mu\text{s}$. Peak intensities were normalized to the value at $\tau_m = 0$. The sample is AV.

processes are not equal due to differences in the spin polarization in the gaseous and adsorbed phases;^{75,76} (ii) signal-to-noise of exchange cross-peaks is much higher in IFHP 2D-EXSY than in CFHP 2D-EXSY; (iii) the gas

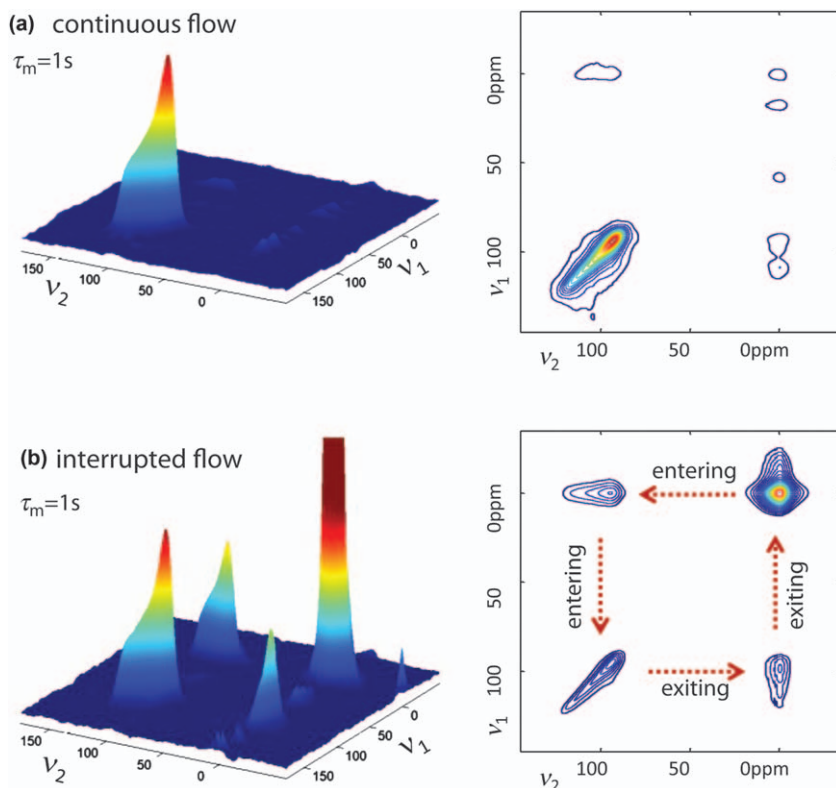


Figure 11.13 HP Xe-129 2D-EXSY spectra of Xe in AV at $-10\text{ }^{\circ}\text{C}$, acquired in (a) CF mode and (b) IF mode with a $\tau_1 = 4\text{ s}$ repolarization delay and a mixing time of $\tau_m = 1\text{ s}$. The gas peak in (b) is cropped. 2D spectra were collected with 100 and 1024 points in the t_1 and t_2 dimensions with a 26 kHz spectral width. Total experiment time for each 2D spectrum was $\sim 65\text{ min}$.

phase diagonal peak is much more intense in the IFHP experiment. At a mixing time of $\tau_m = 1\text{ s}$, cross-peak signals are enhanced by a factor of ~ 60 .

Quantitative determination of kinetic parameters from 2D-EXSY spectra requires high signal-to-noise of cross-peaks,¹⁰⁴ and in this regard, IFHP EXSY is advantageous, particularly in systems with three or more exchanging sites. Mixing times in the IFHP experiment are, in principle, limited only by T_1 inside the channels. The ability to probe longer mixing times enables extension of 2D-EXSY to slower exchange processes or longer diffusion time/length scales in nanochannel systems.

11.5 Hyperpolarized Xe-129 Tracer Exchange

The study of molecular diffusion in uni-dimensional channels using HP Xe-129 was pioneered by Meersmann *et al.*³² Evidence for Xe SFD was

obtained using a CFHP saturation–recovery pulse sequence. The Xe-129 HPTE NMR study provided evidence of single-file diffusion of Xe in polycrystalline TPP.³² Channel adsorbed peak integrals, acquired as a function of the repolarization delay, are normalized to the gas peak integral to remove fluctuations and drift in the hyperpolarization level. The following expressions were proposed to describe the recovery of the signal following rf saturation:³²

$$\frac{S_c(t)}{S_g} = \begin{cases} C_F \int_0^t \tau^{-3/4} e^{-\tau/T_{1c}} d\tau & (11.29) \\ C_D \int_0^t \tau^{-1/2} e^{-\tau/T_{1c}} d\tau & (11.30) \end{cases}$$

The pre-integration factors C_F and C_D were qualitatively shown to be functions of temperature and Xe concentration.³²

11.5.1 Hyperpolarized Tracer Exchange Functions

Meersmann's prefactors can be derived by dividing eqn (11.19) by $N\theta$,

$$\frac{dI_{zc}}{dt} = k_d I_z - k_d I_{zc} - \frac{I_{zc}}{T_{1c}} \quad (\text{adsorbed phase}) \quad (11.31)$$

Eqn (11.31) is adapted to a one-dimensional channel topology by considering the rate of desorption to be diffusion-limited. Assuming doubly open-ended channels (with openings labeled l and r) without blockages, the total desorption rate from any site in the channel will be $k_d = k_{dl} + k_{dr}$, where $k_{dl} = 1/(\tau_l + \tau_0)$, τ_l is the diffusion time to the l opening, and $1/\tau_0$ is the rate of escape over the free energy barrier into the gas phase at the file boundary.

Expressions for τ_r^{-1} are obtained by replacing z by $l - z$. Eqn (11.31) simplifies under experimentally realizable operating conditions. Specifically, at high flow rates (*i.e.* short τ_R) and small n_c/n_g , the spin polarization of the HP gas is negligibly affected by desorption, in which case $dI_z/dt \approx 0$ and $I_z \approx I_{zi}$. Eqn (11.31) becomes

$$\frac{dI_{zc}}{dt} = k_d I_{zi} - (k_d + T_{1c}^{-1}) I_{zc} \quad (11.32)$$

Selective-saturation³³ provides a well-defined initial condition for the magnetization exchange dynamics. Integration of eqn (11.32), taking $I_{zc}(0) = I_{zi}$, yields

$$I_{zc}(t) = I_{zi} \frac{k_d}{k_d + T_{1c}^{-1}} [1 - \exp(-(k_d + T_{1c}^{-1})t)] \quad (11.33)$$

Insertion of equation (11.21) or (11.22) into (11.33) yields the dependence of the Zeeman order on displacement from the channel opening for SFD or

ND, respectively. The total channel-adsorbed signal S_c is obtained by averaging over all displacements up to l ,

$$S_c(t) \propto \bar{I}_{zc}(t) = I_{zi} \frac{1}{\bar{l}} \int_0^l \frac{k_d}{k_d + T_{1c}^{-1}} [1 - \exp(-(k_d + T_{1c}^{-1})t)] dz \quad (11.34)$$

where k_{dl} is given by eqn (11.21) for SFD or eqn (11.22) for ND. The integral in eqn (11.34) simplifies in the “long channel” approximation. For a distribution of channel lengths, the long-channel approximation applies to the shortest channel with length $l_{\min}$ if

$$l_{\min}/2 \gg \sqrt{2F\sqrt{T_{1c}}} \quad \text{or} \quad l_{\min}/2 \gg \sqrt{2DT_{1c}} \quad (11.35)$$

for SFD and ND, respectively. For such channels, hyperpolarization is essentially relaxed before diffusing to the midpoint of the channel, and the upper integral limit can be taken to be infinity:

$$S_c(t) \propto \bar{I}_{zc}(t) = I_{zi} \frac{\bar{n}}{\bar{l}} \int_0^\infty \frac{k_{dl}}{k_{dl} + T_{1c}^{-1}} [1 - \exp(-(k_{dl} + T_{1c}^{-1})t)] dr \quad (11.36)$$

Here, $\bar{n}$ is the ensemble average number of channel openings per channel (ranging from 1 to 2), and $\bar{l}$ is the ensemble average channel length. For SFD, eqn (11.36) takes the form

$$\begin{aligned} \bar{I}_{zc}(t) / (\bar{n}I_{zi}/\bar{l}) &= \int_0^\infty \frac{az^{-4}}{az^{-4} + b} [1 - \exp(-az^{-4} + b)t] dr \\ &= \frac{a}{16b} \left(\frac{b}{a}\right)^{3/4} \left(4\sqrt{2}\pi + \Gamma\left(-\frac{1}{4}\right)\Gamma\left(\frac{1}{4}, bt\right)\right) \\ &= \frac{a}{16b} \left(\frac{b}{a}\right)^{3/4} \left(4\sqrt{2}\pi + \Gamma\left(-\frac{1}{4}\right)\Gamma\left(\frac{1}{4}\right)Q\left(\frac{1}{4}, bt\right)\right) \end{aligned} \quad (11.37)$$

where $\Gamma(1/4, bt)$ is the incomplete gamma and $\Gamma(1/4) = \Gamma(1/4, \infty)$. Using the identity

$$\Gamma\left(-\frac{1}{4}\right)\Gamma(1/4) = -\frac{\pi}{(1/4)\sin(\pi/4)},$$

Eqn (11.37) rearranges to

$$\begin{aligned}
 S_c(t) &\propto \bar{I}_{zc}(t) = I_{zi} \frac{\bar{n}}{\bar{l}} \frac{a}{16b} \left(\frac{b}{a}\right)^{3/4} 4\sqrt{2}\pi \frac{\gamma\left(\frac{1}{4}, bt\right)}{\Gamma\left(\frac{1}{4}\right)} \\
 &= I_{zi} \frac{\pi}{2\Gamma(1/4)} \frac{\bar{n}\sqrt{F}}{\bar{l}} \int_0^t \tau^{-3/4} e^{-\tau/T_{1c}} d\tau \quad (11.38)
 \end{aligned}$$

The analogous derivation for normal diffusion, utilizing eqn (11.22) yields

$$S_c \propto \bar{I}_{zc}(t) = I_{zi} \frac{\bar{n}\sqrt{4\pi D}}{\bar{l}} \int_0^t \tau^{-1/2} e^{-\tau/T_{1c}} d\tau \quad (11.39)$$

While eqn (11.38) provides a convenient analytical form, diffusion dynamics in real single-file systems is probably a lot more complex. Even the RW model with simple inter-particle exclusion interaction (*i.e.* doubly occupancy of lattice sites is forbidden) yields up to four distinct diffusion time regimes (not including ballistic transport at very short t), as discussed in Section 11.2.^{22,23,25} This complexity is further compounded by intermolecular interactions, adsorption barriers, and transport impedances, which may lead to deviations from pure SFD or shift the cross-over between different regimes. Noise in the data also contributes to the errors in fitted parameters, and so it is best to analyze HPTE data in two steps. Firstly, the HPTE data are collected and normalized to the steady-state. Accurate value for the steady-state signal is obtained by copious signal averaging in the fully recovered regime. The normalized data set are then fit to the *NMR tracer exchange curve*, defined as follows:^{34,40}

$$\gamma_{\text{NMR}}(t) \equiv \frac{S_c(t)}{S_c(t \rightarrow \infty)} = \frac{\int_0^t \tau^{a-1} e^{-\tau/T_{1c}} d\tau}{\int_0^\infty \tau^{a-1} e^{-\tau/T_{1c}} d\tau} = 1 - \frac{\Gamma(a, t/T_{1c})}{\Gamma(a)} \quad (11.40)$$

Eqn (11.40) is suitable for analyzing subtle deviations from pure SFD. In sufficiently long channels, where $\langle z^2 \rangle^{1/2}(T_{1c}) \ll \bar{l}$, T_{1c} can be independently measured by thermally polarized NMR (sensitivity permitting), thus eliminating it as a fitting parameter. For times $t \ll T_{1c}$, $S_c(t) \propto t^a$, where a ranges from 0.25 for pure SFD to 0.5 for ND, spin relaxation can be neglected altogether and a remains as the only fitting parameter.

Eqn (11.40) can be applied to the KMC simulations as well. In the KMC simulation of HPTE, relaxation is accounted for by multiplying the spin polarization of each atom in the channel by the exponential relaxation factor

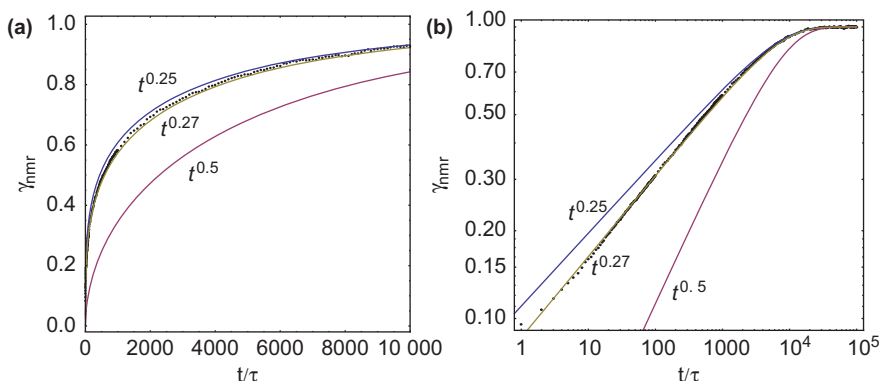


Figure 11.14 (a) KMC simulation of the HPTE curve for an ensemble of 10 000 single-file channels consisting of $L = 201$ lattice sites. A spin-relaxation time of 10 000 time steps was used. Channels were initialized with unpolarized particles at randomly chosen lattice sites with $\theta = 0.7$. Free exchange at the file boundary sites was simulated by tagging any particle occupying a boundary site with the fully polarized particles of the reservoir at each time step. The curves for single-file diffusion ($t^{0.25}$) and Fickian diffusion ($t^{0.5}$) are represented in blue and purple. The best fit of the simulated function to eqn (11.40), which gave $t^{0.27}$, is show in green. (b) Same simulation data on a log plot.

$\exp(-1/T_{1c})$ at each simulation step, where T_{1c} is specified in units of the time step. The analytical model represented by Eqn (11.40) is fit to the KMC simulation in Figure 11.14. Fitting over the full range of the simulation yields a time exponent $\alpha = 0.27$.

In limiting cases where the diffusion is either purely single-file or purely Fickian, extraction of the pre-factor in eqn (11.38) or eqn (11.39) can be achieved by referencing the HPTE-NMR signals to the signals of the HP gas phase, where $S_g \propto n_g I_{zi}$:

$$\frac{S_c(t)}{S_g} = \frac{n_c}{n_g} \langle I_{zc}(t) \rangle \quad (11.41)$$

$$= C_F \int_0^t \tau^{-3/4} e^{-\tau/T_{1c}} d\tau \quad \text{SFD} \quad (11.42)$$

$$= C_D \int_0^t \tau^{-1/2} e^{-\tau/T_{1c}} d\tau \quad \text{ND} \quad (11.43)$$

where

$$C_F = \frac{\bar{n}}{\bar{l}} \frac{\pi\sqrt{F}}{2\Gamma(1/4)} \left(\frac{n_c}{n_g} \right) \quad (11.44)$$

and

$$C_D = \frac{\bar{n}}{\bar{l}} \sqrt{\frac{\pi D}{2}} \left(\frac{n_c}{n_g} \right) \quad (11.45)$$

These are the analytical forms of the Meersmann's prefactors.³² Rearranging eqn (11.44) and (11.45) provides practical relationships for estimating $\bar{l}$ from when the measured quantities n_c/n_g , F and C_F or D and C_D are available.

$$\bar{l} = \frac{\bar{n} \pi}{2\Gamma(1/4)} \left(\frac{\sqrt{F}}{C_F} \right) \left(\frac{n_c}{n_g} \right) \quad (\text{SFD}) \quad (11.46)$$

$$\bar{l} = \bar{n} \sqrt{\frac{\pi \sqrt{D}}{2 C_D}} \left(\frac{n_c}{n_g} \right) \quad (\text{ND}) \quad (11.47)$$

11.5.2 Residence Time Distribution

The residence time distribution $\phi(t)$ can be derived from $\gamma(\tau)$, as discussed in ref. 105.

$$\gamma(\tau) = \int_0^\tau \phi(t) dt, \quad (11.48)$$

where $\phi(t)dt$ denotes the probability that a molecule has entered a single-file channel during the time interval between t and $t + dt$. Solving eqn (11.48) for the tracer exchange curve given in eqn (11.11),

$$\phi(t) = \frac{1}{\bar{l}} \sqrt{\frac{F}{\pi}} t^{-3/4} \quad (11.49)$$

In a HPTE NMR experiment, longitudinal spin relaxation is taken into account in a similar way as discussed in ref. 105 for first-order chemical reactions with $\phi(t)$ given by eqn (11.49). Hence,

$$S_c(t) \propto \int_0^t \phi(\tau) \exp(-\tau/T_{1c}) d\tau = \frac{1}{\bar{l}} \sqrt{\frac{F}{\pi}} \int_0^t \tau^{-3/4} \exp(-\tau/T_{1c}) d\tau \quad (11.50)$$

The same $\sqrt{F}/l$ dependence is obtained as in eqn (11.38). However, the exchange model (*i.e.* eqn (11.19) and (11.20)) is advantageous because of its applicability even when the long channel approximation is not appropriate. The exchange model can be used to fit HPTE-NMR data obtained under operating conditions where the assumptions implicit in the conventional tracer exchange equations are violated. These assumptions depend on spin relaxation time in the bulk, gas flow rate, and channel/gas atom ratio at sorption equilibrium. These variables don't enter into the conventional tracer exchange model.

11.5.3 Selected Hyperpolarized Tracer Exchange Examples

11.5.3.1 Ga Wheels

Metal compounds with a cyclic structure that can be described as a ‘molecular wheel’ have been known for two decades.¹⁰⁶ Among the large family of such wheels are those having a ‘single-strand’ topology with respect to the metal ions, such as $[\text{Ga}_{10}(\text{OMe})_{20}(\text{O}_2\text{CMe})_{10}]$ (abbreviated Ga_{10}). The Ga_{10} wheels have been prepared with empty central cavities, and in the crystal they stack to form supramolecular, nanotubular channels of a monodisperse diameter, as shown in Figure 11.15.

The HPTE NMR curve in the Ga_{10} wheel crystals measured at a Xe pressure of 667 mbar is shown in Figure 11.16. Least squares fits to eqn (11.40), letting a and T_{1c} vary, are shown as the solid black curves. The two parameter fits yielded $a = 0.33 \pm 0.01$ and $T_{1c} = 1.4 \pm 0.1$. The red and blue traces are the best fits to eqn (11.40) fixing a to 0.5 and 0.25, respectively. The fitting results indicate diffusion which is close to pure SFD for $\tau \geq 50$ ms. Notably, the spin-lattice relaxation for ^{129}Xe in the gallium wheels is significantly shorter than in other diamagnetic single-file nanotube materials such as AV^{33} and TPP^{32} . Such a drastic reduction in T_{1c} is most likely due to paramagnetic in the metal precursors used in the synthesis.

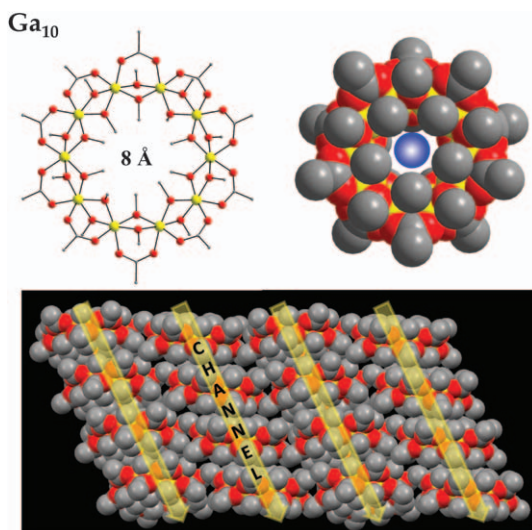


Figure 11.15 $\text{Ga}_{10} = [\text{Ga}_{10}(\text{OMe})_{20}(\text{O}_2\text{CMe})_{10}]$. Counterions have been omitted for clarity. Color code: Ga, yellow; O, red; N, green; C, gray; Xe, blue. The internal channel diameter is about 8 Å. In comparison, the Xe atom (in blue) has a collision diameter of 4.4 Å, thus satisfying the single-file criterion in Ga_{10} channels.

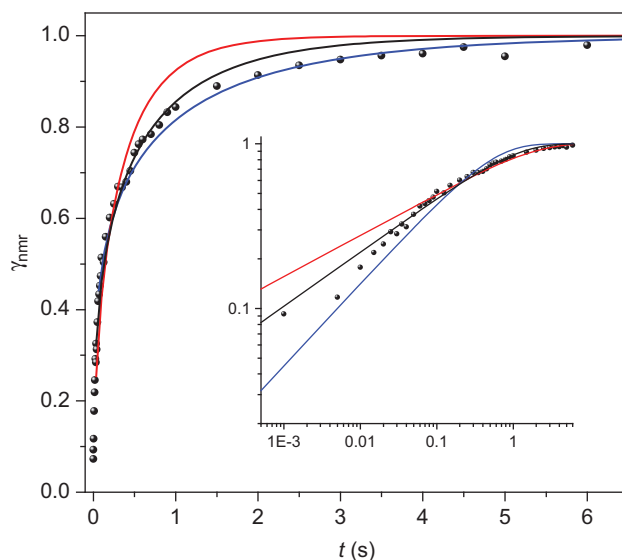


Figure 11.16 CFHP ^{129}Xe NMR tracer exchange data at 25 °C in crystalline Ga_{10} wheels at a Xe partial pressure of 667 mbar in a Xe/He mixture with a total pressure of 4000 mbar. Inset: same data on log-log scale. Black trace: best fit to eqn (11.40) allowing T_{1c} and a to vary as fitting parameters. Red trace, $a = 0.5$, T_{1c} varying; blue trace: $a = 0.25$, T_{1c} varying.

11.5.3.2 *L-Ala-L-Val*

SEM images of an AV sample *as received* from MP Biomedicals, shows whisker-shaped crystals with lengths ranging from about 10–100 μm (Figure 11.17a). An SEM image of a portion of the as-received sample after pulverizing (pAV) in a mortar and pestle is shown in (Figure 11.17b). Following evacuation at high vacuum for several hours, the fully relaxed, thermally polarized ^{129}Xe spectra of AV and pAV were recorded under 3 bar Xe. Both spectra exhibit symmetrically shaped adsorbed phase signals centered at a chemical shift of 140 ppm (referenced to Xe gas extrapolated to zero pressure¹⁰⁷). However, both the gaseous and adsorbed phase lines are significantly broader in the spectrum of pulverized AV. Yet the ratio of the signals, which gives the relative number of adsorbed and gas phase Xe atoms, n_c/n_g , did not change significantly, indicating that the specific sorption capacity was not affected by the pulverization.

Xe-129 HPTE curves obtained in both AV and pAV are in near-perfect agreement with the pure SFD model at all t . Figure 11.18 present the results for pAV along with non-linear least-squares best fits to eqn (11.40), which gave $a = 0.24 \pm 0.01$.

Eqn (11.8) predicts a cross-over to CM diffusion under PFG NMR conditions.^{22,23} Taking $\lambda \approx c/3 \approx 0.33$ nm (corresponding to a capacity of ~ 3 Xe atoms per c-translation of the unit cell), $\bar{l} = 6.2$ and $\theta = 0.35$, the cross-over is estimated to occur at displacements of ≈ 50 nm for hollow, doubly

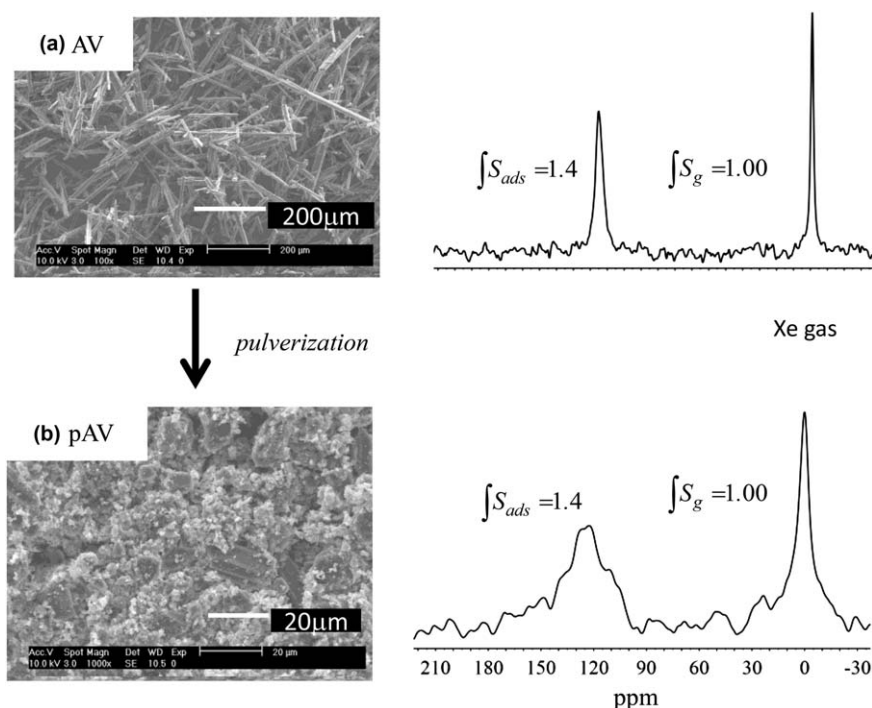


Figure 11.17 Fully relaxed, thermally polarized ¹²⁹Xe NMR spectra of Xe adsorbed in AV at a Xe pressure of 3 bar and O₂ pressure of 200 mbar. Spectra were acquired at 9.4 T using a single 3.5 μs pulse. Integrals of the adsorbed phase peaks relative to the gas phase are indicated. 32 transients were averaged using a 30 min recycle delay.

open-ended AV channels. The HPTE-NMR experiments probes displacements up to $\sim 3.5 \mu\text{m}$, yet no indication whatsoever of any transition $\gamma_{\text{nmr}} \propto t^{1/4} \rightarrow t^{1/2}$ stemming either from mutual passages within the nano-channels or as a consequence of CM diffusion is detected. This is consistent with KMC simulations which exhibit no deviation from the $\gamma(t) \propto t^{0.25}$ time-scaling at the cross-over time given in eqn (11.8).

The coefficients C_F are extracted with the help of eqn (11.42) using each of the following three methods: (1) linear least squares fit of $\log(s_c(t)/s_g)$ vs. $\log t$ to the data at short t yields an intercept $\log(4C_F)$, which obviates information about T_{1c} ; (2) acquisition of the steady-state (SS) signal ratio which is related to C_F by $s_c(\infty)/s_g = C_F T_{1c}^{1/4} \Gamma(1/4)$; (3) non-linear least squares fitting of $s_c(t)/s_g$ to the data over the full range of t with C_F as a fitting parameter.

The compliance to the SFD model over the entire observable time range (*ca.* 10 ms–100 s) is nearly perfect. Under such conditions, the mean open channel persistence length $\bar{l}$ can be estimated using C_F values estimated from HPTE-NMR data together with F values determined in separate PFG-NMR experiments³⁶ and the n_c/n_g ratio obtained from fully-relaxed, thermally polarized NMR spectra.⁴⁰ Mean channel lengths $\bar{l}$ for the

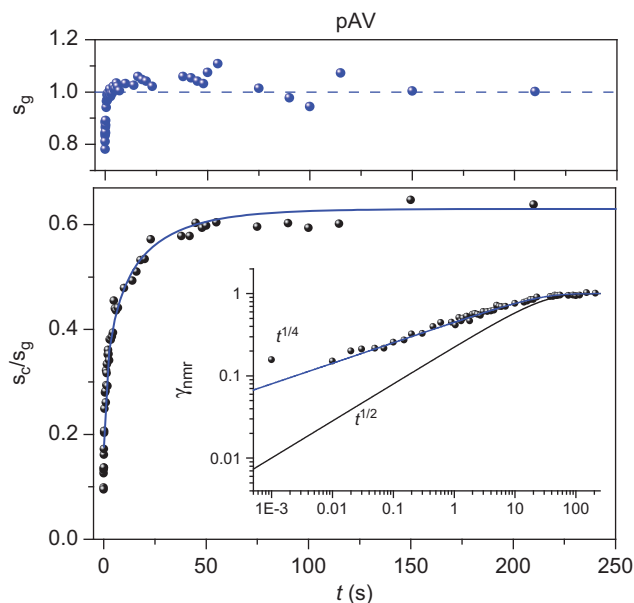


Figure 11.18 ^{129}Xe HPTE NMR signals (referenced to the gas phase signal) acquired in pAV at 298 K using 3 bar Xe at $\sim 100 \text{ mL min}^{-1}$. The blue curve shows the best fits to eqn (11.42) taking C_F as the fitting parameter. The blue symbols in the upper panel represent the normalized gas phase signal. Inset: log-log representation of the normalized tracer exchange data (black spheres) together with best fit to eqn (11.40) yielding $a = 0.24$ for the fitting parameter. The solid black curve represents $\gamma_{\text{nmr}}(t)$ with $a = 0.50$.

as-received and pulverized AV specimens (assuming $\bar{n} = 1$) are estimated as $50 \pm 10 \text{ }\mu\text{m}$ and $6.6 \pm 0.3 \text{ }\mu\text{m}$, respectively. The values are comparable to the crystallite lengths seen in the SEM images. It should be noted, however, that since $\bar{n}$ is an unknown quantity, $\bar{l}$ could be greater by up to a factor of 2 (if all channels are doubly open ended).

The results suggest that the crystals in the AV and p-AV specimens are effectively hollow all the way through with defect densities per unit channel length estimated to be less than 10 ppm. By pulverizing the AV, the open channel length was effectively reduced from $50 \text{ }\mu\text{m}$ to $6.6 \text{ }\mu\text{m}$. The particles seen in the pulverized sample appear to be at most $5 \text{ }\mu\text{m}$ in size, suggesting most of the channels are blocked at one end.

11.6 Summary

Computational studies confirm that the complexity of transport in real molecular single-file materials is compounded by existence of desorption barriers, blockages, clustering, long-range interactions, and momentum damping effects.^{3,4,6,22,23,27,86,108–115} Furthermore, in a sample consisting of a mixture of channels with one or two openings, the observed tracer

exchange curve would represent a superposition of the two types of tracer exchange curves, and the overall time-scaling at long observation times would be somewhere intermediate between t^0 and t^1 time-scaling. The factors may suppress, enhance or shift the transitions between different diffusion regimes.

Adherence to the simple analytical expressions for HPTE also depends on the extent to which the assumptions used to derive them are fulfilled under the actual experimental conditions. A primary assumption is that the polarization of the gas phase is unaffected by exchange. When a large excess of HP gas exists, this approximation will be excellent. For tightly packed porous media with low void space, very high relative adsorption, and fast exchange, the assumption may be not so good, and it then becomes necessary to work with the system of coupled equations describing exchange of magnetization between the phases. As can be seen in the HPTE data presented in Figure 11.18, the gas phase signal is momentarily reduced by about 20% relative to the steady-state value at short recovery times. However, it recovers quickly and appears to have minimal overall effect.

The relative importance of all of the aforementioned factors will obviously vary with the specific physical and chemical characteristics of the channel material and the diffusing sorbate species. Hence, the high degree of compliance obtained in some systems (*e.g.* AV) with the simple SFD model is truly remarkable. In other systems that have been studied by the same technique, such as Ga₁₀ wheel nanotubes or VA, SFD gives an overall better fit to the HTSE data than does ND, particularly at longer observation times, but deviations are seen at shorter times (*ca.* below 100 ms). In attempting to interpret such results, it is important to take note of the approximations used in the simple analytical models. Furthermore, the simple models applied herein do not consider the possibility of diffusion dynamics leading to variations in the time-scaling of the MSD.

Single-file diffusion has intriguing potential applications to separations and catalysis, where it will be crucial to fine-tune the diameter of the channel with respect to the size of the components in the mixture. Control of channel persistence length and length monodispersity is difficult to achieve for both supramolecular chemistry and top-down nanomaterials fabrication approaches. Moreover, functionalization to incorporate specific catalytic active sites adds yet another level of complexity. These tasks remain as non-trivial challenges to materials science.

This chapter has introduced hyperpolarized NMR methodology with experimental demonstrations to several types of one-dimensional nanochannel materials. Hyperpolarized Xe-129 NMR is well-suited for diffusion studies in nanomaterials due to the combination of high detection sensitivity and high sensitivity to the electronic environment. Alternative hyperpolarization methods (*e.g.* dissolution dynamic nuclear polarization¹¹⁶ or parahydrogen induced polarization^{117–120}) could facilitate tracer exchange methodology to other nuclei, such as carbon-13, fluorine-19 or nitrogen-15, thereby substantially expanding its applicability. The use of sorbates

supporting long-lived nuclear spin states¹²¹ would significantly extend the diffusion time-scales that could be followed by hyperpolarized tracer exchange NMR.

Unfortunately, realistic molecular dynamics simulations are unable to provide access to the time or length-scales of interest in real single-file systems due to computational limitations. Thus, fundamental studies will continue to rely mainly on experimental results. The capabilities of HP Xe-129 NMR based techniques, some of which have been highlighted in this chapter, can advance our understanding of molecular transport in the single-file regime.

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Studies of Metal–Organic Frameworks: Xenon for Probing Framework Porosity, Breathing and Gating Behavior

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12.1 Introduction

The synthesis and characterization of metal–organic frameworks (MOFs) has become a rapidly evolving field over the past 15 years.^{1–6} MOFs represent an entirely new class of crystalline porous solids with interesting properties such as extraordinarily high specific surface area and gas storage capacity. For example, MOF-210⁷ provides a BET surface area of 6240 m² g^{−1}, a pore volume of 3.6 cm³ g^{−1}, and a crystallographic density of only 0.25 g cm^{−3}. In contrast, the crystalline and purely inorganic zeolite L⁸ exhibits a BET surface area of 344 m² g^{−1} and a total pore volume of 0.25 cm³ g^{−1} at a density of 2.1 g cm^{−3}. This corresponds to an 18-fold higher specific surface area and a 15-fold higher specific pore volume for the MOF! Metal–organic frameworks are hybrid materials. They are composed of an organic part, so-called linkers, interconnecting the inorganic secondary building units (SBUs) (see Figure 12.1). Usually, the SBUs contain one or more metal ions

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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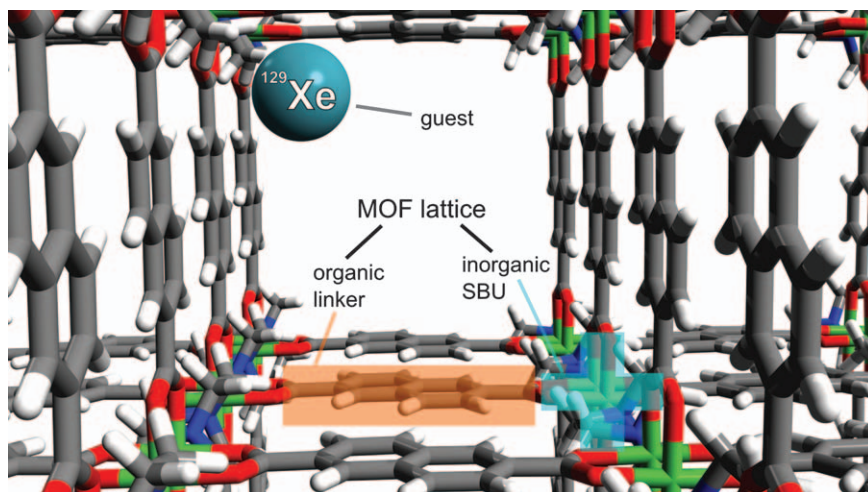


Figure 12.1 Schematic representation of the MOF lattice (here: DUT-8(Ni)²⁶), consisting of organic linkers and inorganic SBUs. The MOF serves as a host structure for guests such as ¹²⁹Xe within the void spaces (for example pores or channels). C: grey, H: white, N: blue, O: red, Ni: green, Xe: cyan. Reproduced from Hoffmann *et al.*³¹

such as Cu²⁺, Ni²⁺, Zn²⁺, Al³⁺, or Zr⁴⁺ coordinatively bound to atoms such as oxygen. These metal-oxide clusters are bridged, that means, interconnected by multifunctional organic linkers. For many MOFs, the metal-oxide clusters are discrete, *i.e.*, the inorganic substructure is 0-dimensional (0D).⁵ However, metal-oxides can also form more complex inorganic SBUs.^{2,5} The SBUs can, for example, consist of inorganic chains leading to a 1D inorganic substructure. Even 3-dimensional (3D) inorganic sublattices can be formed.

In contrast to other one- or two-dimensional coordination polymers, the relatively strong coordinative interactions between linkers and inorganic building units often result in “open” three-dimensional networks exhibiting micro- or mesopores. This allows the adsorption of various guest molecules within the resulting pore system. Numerous possible future applications of MOFs can be envisioned in the field of gas storage,^{9,10} gas and solvent purification,^{11–13} and (enantioselective)^{14–17} catalysis.^{18–20} Some MOFs exhibit uncommon properties such as nonlinear optical characteristics,²¹ magnetic spin frustration,²² magnetic coupling of paramagnetic metal centres²³ as well as other unusual magnetic, optical, and electronic effects. Therefore, MOFs are assumed to be potentially useful for further applications, *e.g.* in molecular sensing²⁴ and for optical purposes.

Traditional porous materials such as zeolites, activated carbons, mesoporous silica, and the majority of MOFs, exhibit rigid lattices which do not change their overall structure during the adsorption/desorption of guest molecules. In contrast to this conventional behavior, some MOFs such as

MIL-53,²⁵ DUT-8(Ni), or DUT-8(Co)^{26,27} exhibit a flexible network. These compounds undergo reversible structural transformations during the adsorption/desorption of appropriate guests like hydrocarbons, nitrogen, carbon dioxide, or xenon. This interesting effect is denoted as breathing or the accordion effect and attracts increasing interest.²⁸ If the pores are entirely inaccessible for a particular guest in the narrow-pore state, the adsorbed amount of this guest is practically zero below the so-called gate-opening pressure. Beyond the gate-opening pressure, the structure of the MOF suddenly opens, leading to a collaborative unblocking of the pores. This can be seen in corresponding adsorption isotherms since the uptake of guest molecules suddenly rises at this pressure. MOFs exhibiting this effect²⁹ are known as gate-pressure MOFs. The structural changes for gate-pressure MOFs are associated by a more or less pronounced hysteresis during the adsorption/desorption process. The gate opening pressure as well as the closing behavior depends on the pressure, temperature and characteristics of the guest. That means, the structure remains open during pressure release even below the gate-opening pressure—provided the pore system has been opened before. It should be noted that the breathing process can be accompanied by dramatic changes of the unit cell volume. For example, the unit cell volume of the activated MIL-88C almost triples during pyridine adsorption.³⁰

12.2 ¹²⁹Xe NMR of Non-flexible MOFs

NMR spectroscopy is well suited to study both the MOF lattice itself as well as host–guest interactions between the MOF and adsorbed species such as xenon or other species.^{31–34} The first application of ¹²⁹Xe NMR spectroscopy to a MOF was reported in 2006.³⁵ Subsequently, ¹²⁹Xe NMR spectroscopy has been employed for investigations of a number of other interesting MOF systems.^{26,36–39}

As already explained in detail in previous chapters, the overall chemical shift of adsorbed ¹²⁹Xe consists of various contributions:^{40,41}

$$\delta = \delta_0 + \delta_S + \delta_{\text{Xe-Xe}} + \delta_{\text{SAS}} + \delta_E + \delta_M \quad (12.1)$$

Here, δ_0 denotes the chemical shift of xenon gas at a xenon density of zero (reference) and δ_S is the chemical shift contribution due to xenon-surface interactions. The influence of strong adsorption sites is described by the term δ_{SAS} . In the presence of cationic species inside the pores, the chemical shift is influenced by the resulting electric fields giving rise to the contribution δ_E . If the compound exhibits paramagnetic sites, a paramagnetic shift contribution δ_M must be taken into account. Moreover, the chemical shift is strongly influenced by xenon–xenon interactions. The resulting term $\delta_{\text{Xe-Xe}}$ depends on the xenon density ρ_{Xe} and can be written as $\delta_{\text{Xe-Xe}} = \Delta_{\text{Xe-Xe}} \rho_{\text{Xe}}$. Here $\Delta_{\text{Xe-Xe}}$ denotes the slope of $\delta_{\text{Xe-Xe}}$. Within the present chapter, we include further possible contributions due to electric fields and strong adsorption sites in the term δ_S . Inverse correlations between free path and δ_S are well known for silica-based materials⁴² and in particular for

zeolites,⁴³ *i.e.*, δ_S increases with decreasing free pore volume (for more details, see chapter 1).

In order to illustrate some important effects observed by ^{129}Xe NMR spectroscopy on MOFs, the ^{129}Xe NMR spectra of the non-flexible UMCM-1⁴⁴ during an isothermal xenon adsorption experiment at room temperature should be briefly discussed (see Figure 12.2). Importantly, it should be noted

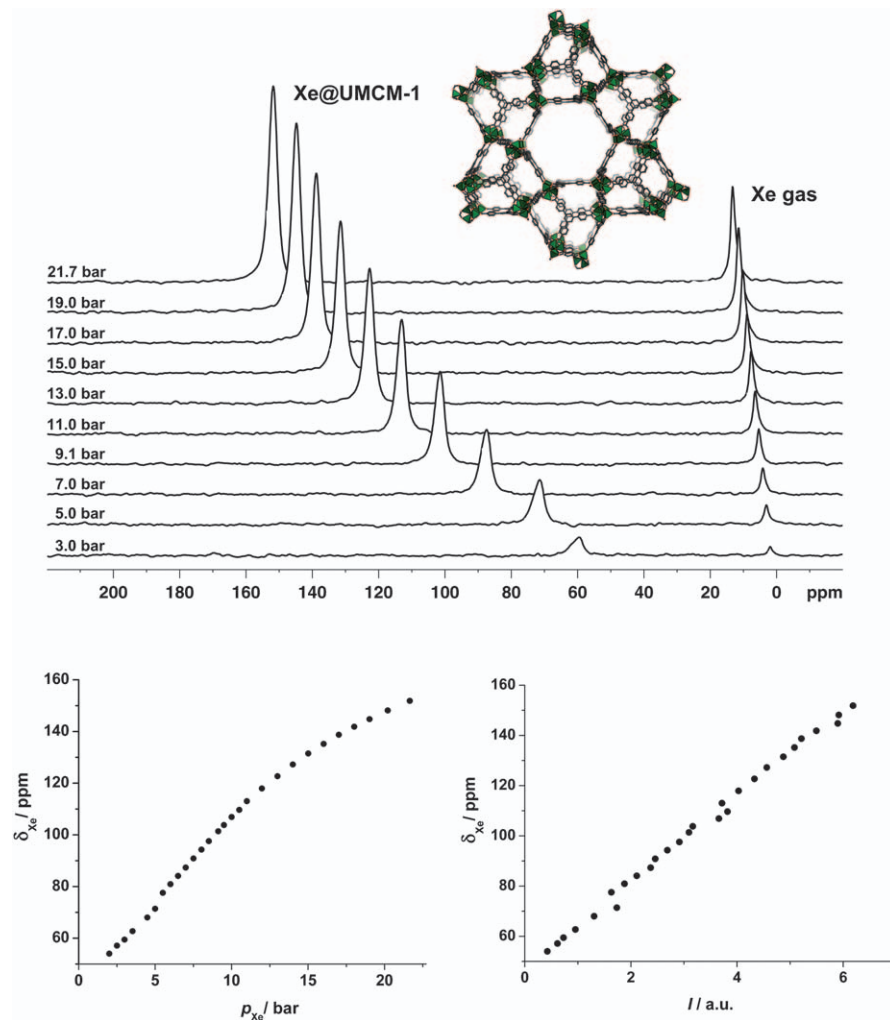


Figure 12.2 Top: ^{129}Xe NMR spectra of xenon adsorbed on UMCM-1 measured at room temperature (r.t.) for various pressures. UMCM-1 exhibits xenon-accessible, well interconnected micro- and mesopores (see the scheme representing this structure). Bottom: ^{129}Xe NMR chemical shift of xenon adsorbed on UMCM-1 measured at r.t. as a function of pressure (left) and xenon signal intensity (right). Reproduced from Hoffmann *et al.*³¹

that UMCM-1 possesses two different types of pores, namely micro- and mesopores. The diameter of the micropores amounts to *ca.* 1.4 nm, whereas the mesoporous channels are *ca.* 3.1 nm wide. The relative contributions to the total pore volume amount to *ca.* 2/3 and 1/3 for the micro- and mesopores, respectively. Moreover, the pore windows are rather large. That means both-micropores and the mesopores-should be easily accessible for xenon with its diameter of 0.44 nm. However, only one single signal due to $^{129}\text{Xe}@UMCM-1$ is detectable. It is, therefore, concluded that the xenon atoms rapidly exchange between both types of the pores which are well interconnected to each other. δ_0 is set to $\delta_0=0$ at an extrapolated pressure of 0 bar, which is the commonly used referencing method. It should be noted that the chemical shift of the gaseous ^{129}Xe correlates linearly with the xenon pressure within the applied pressure range of up to 20 bar.³¹ The xenon pressure is approximately proportional to the density at room temperature and within this pressure range. The observed behavior is, therefore, in excellent agreement with the prediction of a linear interdependence between the chemical shift and the xenon density up to *ca.* 100 amagat.^{45,46} Although the signal is narrow and symmetric at higher xenon pressures, it exhibits a progressing anisotropy below *ca.* 5 bar xenon pressure (see Figure 12.3). Two possible explanations exist for this phenomenon: (i) it may be due to the anisotropic local environment of xenon inside the pores as previously described Springuel-Huet and Fraissard⁴⁷ (ii) it is possible that the exchange between the micro- and mesopores becomes slower at decreasing pressure. This could explain the observation of a corresponding “shoulder” at higher chemical shift.

Furthermore, the intensity of the signal due to $^{129}\text{Xe}@UMCM-1$, *i.e.*, xenon adsorbed in the pore system, as well as its chemical shift increase because of the growing xenon density ρ_{Xe} inside the pore system with increasing xenon pressure (see Figure 12.2). An almost linear interdependence between the chemical shift of $^{129}\text{Xe}@UMCM-1$ and the applied pressure is found up to *ca.* 12 bar under the chosen conditions (see Figure 12.2, bottom left). Application of higher pressures induces a progressively decreasing slope of the curve. The signal intensity of $^{129}\text{Xe}@UMCM-1$ can be used as a measure for the xenon concentration inside the UMCM-1 pore system. Hence, the ^{129}Xe NMR chemical shift of $^{129}\text{Xe}@UMCM-1$ should be linearly correlated with the signal intensity according to eqn (12.1), in agreement with the observed behavior (see Figure 12.2, bottom right). This proves the validity of the equation $\delta_{\text{Xe-Xe}} = \Delta_{\text{Xe-Xe}} \cdot \rho_{\text{Xe}}$ also for adsorbed xenon under the aforementioned experimental conditions. Acquisition of the ^{129}Xe NMR spectra at low relative pressures of xenon allows the extrapolation of the measured chemical shift due to $^{129}\text{Xe}@UMCM-1$ to zero signal intensity, *i.e.*, zero xenon density. This procedure yields $\delta(0) = 49 \pm 3$ ppm. Since UMCM-1 does not contain paramagnetic sites, $\delta(0)$ is equal to the contribution δ_s due to interactions between xenon and the inner surface of UMCM-1 (see eqn (12.1)).

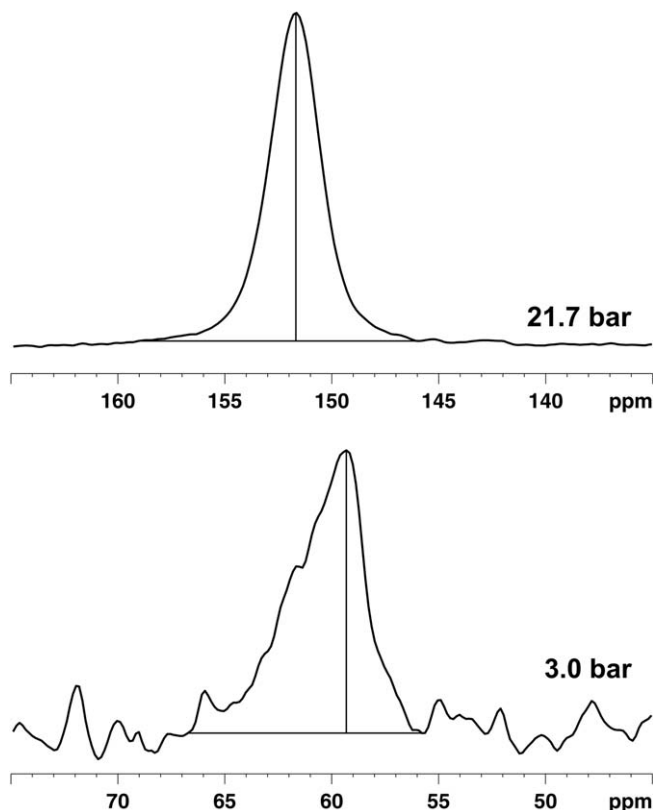


Figure 12.3 ^{129}Xe NMR signals of Xe@UMCM-1 measured at r.t. and different pressures. Reproduced from Hoffmann *et al.*³¹

12.3 ^{129}Xe NMR of Flexible MOFs

In the case of flexible MOFs, the pores and/or their “entry windows” are changed if the crystal structure switches. The flexibility of the MOF lattice can be explored using a guest like ^{129}Xe as a sensitive probe for changes of the porous host structure during its breathing transitions. For example, ^{129}Xe NMR spectroscopy turned out to be useful for sensing structural changes in the MOF compounds MIL-53³⁶ and DUT-8.^{27,39}

The gate-pressure MOF DUT-8(Ni) is a material with a very pronounced gate-pressure effect during adsorption of several gases such as carbon dioxide, butane, and xenon.^{26,27} It should be noted that the adsorption behavior below the temperature-dependent gate-opening pressure depends on the sample pretreatment conditions.³⁹ The pore system was found to be entirely inaccessible for xenon if the solvent was removed from the as-synthesized sample by solvent exchange with subsequent supercritical drying using CO_2 .⁴⁸ Without supercritical drying, the samples are in a narrow-pore state which allows the penetration of limited amounts of xenon

even below the gate-opening pressure.²⁶ This has been shown by isothermal volumetric xenon adsorption measurements.³⁹ In excellent agreement with these observations, only the gas phase signal is observed in the ^{129}Xe NMR spectra below the gate-opening pressure samples after drying in supercritical CO_2 (see Figure 12.4). Beyond the gate-opening pressure of *ca.* 12 bar at 237° K, a further signal occurs at *ca.* 227 ppm. This is due to xenon adsorbed in the pore system DUT-8(Ni). That means the MOF structure collectively opens at the gate-opening pressure and high amounts of xenon are then adsorbed as can be seen in the high-pressure *in situ* ^{129}Xe NMR spectra (see Figure 12.4).³⁹ The chemical shift of $^{129}\text{Xe}@DUT-8(\text{Ni})$ remains almost constant at higher pressures. It amounts to 229 ppm at the highest applicable pressure, *i.e.*, the liquefaction pressure of xenon. This constant chemical shift indicates that the xenon density ρ_{Xe} inside the pore system of open DUT-8(Ni) particles and the overall pore structure must remain practically constant during further pressure increase (*cf.* eqn (12.1)). This shows that the structure opening is accompanied by immediate and complete pore filling. Afterwards, further pressure increase results only in minor changes. The chemical shift of $^{129}\text{Xe}@DUT-8(\text{Ni})$ even exceeds that of liquid xenon (203 ppm at 237° K, see Figure 12.4). Such high chemical shifts are indicative of a high, liquid-like xenon density ρ_{Xe} within the DUT-8(Ni) pores. The density of xenon inside the fully occupied pore system could

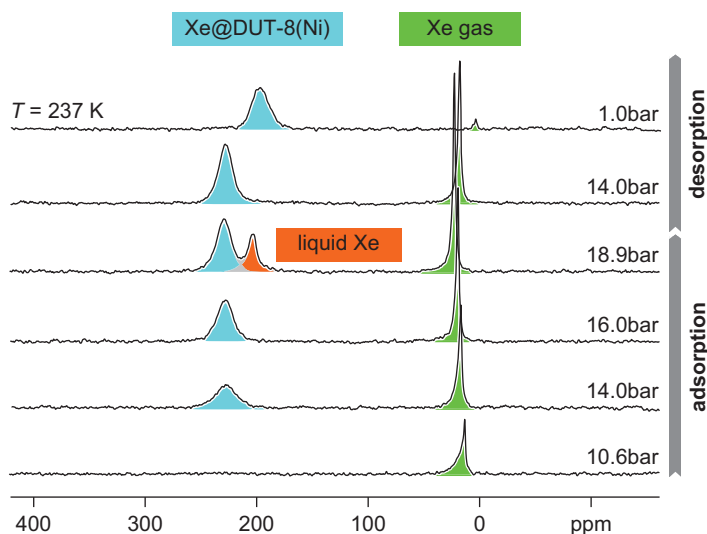


Figure 12.4 ^{129}Xe NMR spectra of DUT-8(Ni)³⁹ pressurized with various amounts of xenon, measured at 237° K. Note that the sample was dried using supercritical CO_2 and activated in high vacuum prior to the measurement. The initially closed structure opens during the adsorption experiment at a gate-opening pressure of *ca.* 12 bar whereas it remains open during desorption down to 1 bar (hysteresis). Reproduced from Hoffmann *et al.*³¹

be estimated: The pore volume of $0.99\text{ cm}^3\text{ g}^{-1}$ determined by computer simulations using the non-adsorbing noble gas helium as a probe agrees remarkably well with the experimentally determined total pore volume of $1.05\text{ cm}^3\text{ g}^{-1}$ (N_2 physisorption, $T = 77\text{ K}$, $p/p_0 = 0.95$). Xenon concentrations of 25 xenon atoms per unit cell (Xe/u.c.) and 22 Xe/u.c. were derived from grand-canonical Monte-Carlo (GCMC) simulations and the xenon adsorption isotherm, respectively.³⁹ These values correspond to xenon densities inside the pore system of 2.52 g cm^{-3} and 2.34 g cm^{-3} , respectively. The density of liquid xenon amounts to 2.94 g cm^{-3} at 1.01 bar and 165° K . That means the xenon densities observed in the pore system of DUT-8(Ni) are indeed close to the liquid state. Note that a possible paramagnetic contribution due to the Nickel atoms may further enhance the chemical shift. It is very remarkable that the signal due to adsorbed xenon remains almost constant during pressure release (desorption) even below the gate opening pressure. This observation shows that there is almost no desorption during pressure release—until the structure immediately closes at very low pressures. This pronounced hysteresis is another characteristic property of gate-pressure MOFs such as DUT-8(Ni).

12.4 Computer Simulations

Computer simulations are a valuable tool for a better interpretation of the experimental data on the molecular scale. In particular, breathing effects as well as interactions between host lattice and guests—such as xenon—can additionally be simulated.^{49,50} Molecular dynamics (MD) simulations were carried out in order to further understand the gating behavior of DUT-8(Ni). The open structure of DUT-8(Ni) is only experimentally observed for as-synthesized or re-solvated, *i.e.*, solvent-filled samples and for DUT-8(Ni) filled with adsorbed gas atoms or molecules such as xenon beyond the gate-opening pressure. The empty, activated DUT-8(Ni) exhibits a “closed” structure in the temperature range studied yet (77 K to *ca.* 300 K). Therefore, GCMC simulations have been utilized to simulate the influence of xenon gas at certain pressures upon the open structure with an external xenon pressure of 1 bar at 230 K . It should be noted that DUT-8(Ni) shows the above-described hysteresis during pressure release after the structure has been opened beyond the gate pressure (see Figure 12.4). The structure stays open even at a xenon pressure of just 1 bar at 237 K . GCMC simulations³⁹ predict a xenon loading of 19 Xe/u.c. for the open structure at a xenon pressure of 1 bar and a temperature of 230° K . This is close to the maximum xenon concentration of 22 Xe/u.c. determined by volumetric adsorption experiments at 165° K .^{26,39} Therefore, 19 Xe/u.c. were added to the open DUT-8(Ni) structure in the corresponding simulations and the structure was then subjected to geometry optimization. The structure remained open (see Structure 4 in Figure 12.5) in agreement with the experimental observations described above. Furthermore, three preferred adsorption sites could be localized for xenon. They exhibit adsorption energies of 25 kJ mol^{-1} ,

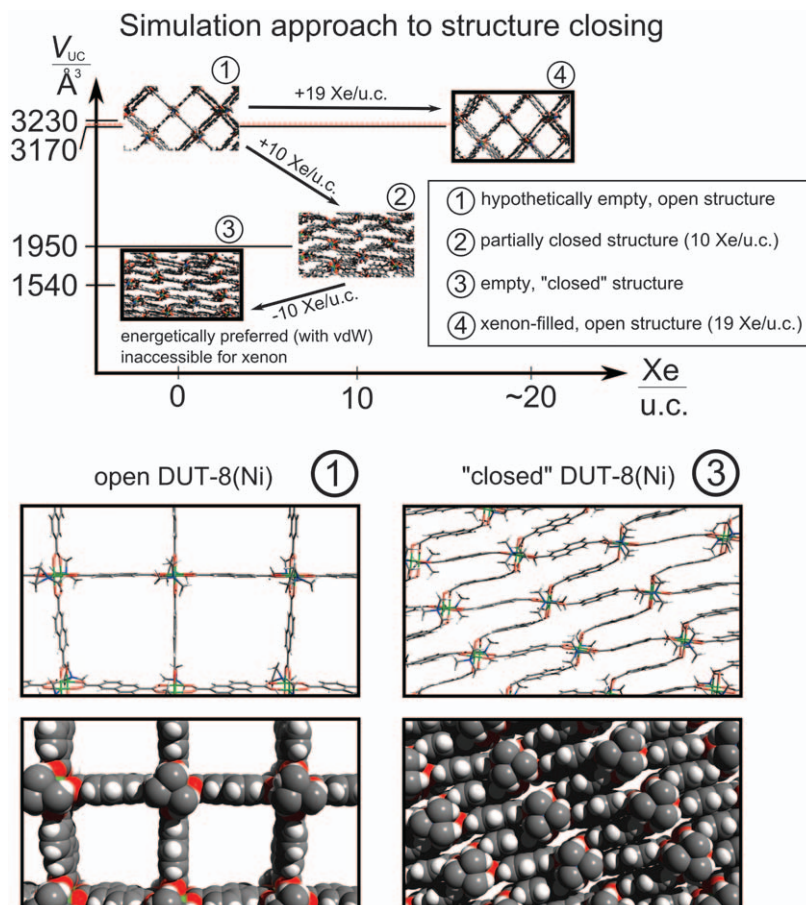


Figure 12.5 Top: Scheme of the computational approach for observing the closure of the DUT-8(Ni) structure. Starting point is the experimentally determined open structure²⁶ after relaxation (Structure 1). If Structure 1 is loaded with an amount of xenon corresponding to the predicted adsorption capacity (19 Xe/u.c.), it remains open and the volume of the unit cell only drops slightly (Structure 4). If 10 Xe/u.c. are put into Structure 1, MD simulations result in a partially closed structure (Structure 2). Subsequently, xenon is totally removed from this hypothetical transition structure. MD simulations then result in Structure 3. It is important to note that the "closed" Structure 3 is only stable if DFT-vdW is applied. Without the inclusion of van der Waals forces, Structure 1 is energetically favored instead of Structure 3. The unit cell volumes for Structures 1 and 3 are shown for the geometrically optimized unit cells. Red, dashed line: unit cell volume of $3190 \text{ \AA}^3 \text{ u.c.}^{-1}$ for the experimentally determined open structure. Bottom: Comparison of experimentally determined open and predicted "closed" structure of DUT-8(Ni) in stick design (top) and van der Waals illustration (bottom), respectively. Nickel, hydrogen, carbon, nitrogen and oxygen atoms are shown in green, white, grey, blue and red, respectively. Xenon atoms are omitted for clarity. Reproduced from ref. 39 with permission from the American Chemical Society.

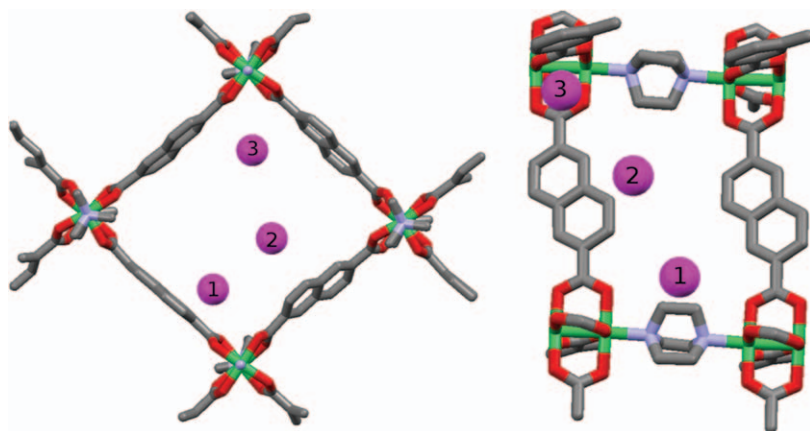


Figure 12.6 Preferred adsorption sites for xenon in the unit cell of DUT-8(Ni) as predicted by MD simulations, (1) close to the pillar ligand dabco, (2) nearby the 2,6-ndc linker, and (3) between two nickel atoms at the paddle wheel unit. The atoms are shown in the same colors as in Figure 12.1. Xenon atoms are shown in pink. Hydrogen atoms are omitted for clarity.

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17 kJ mol^{-1} , and 7 kJ mol^{-1} . The corresponding predicted adsorption sites are shown in Figure 12.6.

As described above, the ^{129}Xe NMR spectroscopic data as well as the volumetric adsorption measurements show that the structure closes if the xenon atoms are removed, *i.e.*, for zero loading. This structure closing process could also be simulated. This was done by reducing the amount of xenon inside the open structure in the computer simulation. For a xenon loading of 10 Xe/u.c., MD simulations revealed a considerable shrinkage of the structure: The unit cell volume reduces by *ca.* 40% from a volume of $3230 \text{ \AA}^3$ to $1950 \text{ \AA}^3$ (Structure 2 in Figure 12.5). In reality, structure closing is a rather concerted effect which is accompanied by rapid xenon desorption. That means the calculated partially xenon-loaded structure (10 Xe/u.c.) should be considered as a hypothetical intermediate state. In contrast to the experiment, the number of xenon atoms put into the DUT-8(Ni) structure is kept constant within the computed ensemble (constant number of atoms, constant pressure, and constant temperature) used for the MD simulations. After removal of the remaining 10 Xe/u.c. from the partially closed computed structure (Structure 2 in Figure 12.5), a subsequent relaxation of the structure has been performed in the MD simulations. This finally resulted in a completely closed structure, *i.e.*, a further unit cell contraction down to a final volume of $1540 \text{ \AA}^3$ for the empty structure. This corresponds to *ca.* 50% of the volume of the fully opened xenon-loaded structure. In agreement with our experimental observations, this simulated “closed” structure is also found to be totally inaccessible for xenon within the corresponding GCMC

simulations (see Structure 3 in Figure 12.5, bottom). Density-functional theory calculations including van der Waals interactions (DFT-vdW) predict a state of lower energy for the empty “closed” DUT-8(Ni) compared to the hypothetical empty open DUT-8(Ni) (Structure 1 in Figure 12.5). This energy mainly arises from the interactions between the linker molecules, in particular, π - π stacking interactions (see below).³⁹ The energy difference of 136 kJ (mol u.c.)⁻¹ explains the experimental observation that DUT-8(Ni) prefers the “closed” state below the gate-opening pressure. Beyond the gate-opening pressure, the adsorption enthalpy of the adsorbed guest molecules, *i.e.*, the contribution due to host-guest and guest-guest interactions has to overcompensate the energy difference of 136 kJ (mol u.c.)⁻¹ between the empty open and closed structure. Importantly, the empty “closed” structure was only energetically preferred if van der Waals interactions are explicitly included within the DFT calculations (DFT-vdW).⁵¹ This is in good agreement with DFT calculations on MIL-53(Cr)⁵² without further dispersion corrections. The narrow pore state was always not stable in these calculations, although thermodynamic measurements suggest a narrow pore state for the MIL-53 family at 0 K.⁵³ In analogy, the empty “closed” structure of DUT-8(Ni) is also unstable if DFT is exerted in local density approximation (LDA) or generalized gradient approximation (GGA). Therefore, the explicit inclusion of host-host van der Waals interactions is absolutely crucial for the simulation of the gating process of DUT-8(Ni). In particular, the 2,6-ndc linkers considerably contribute to the stabilization of the “closed” structure by π - π -stacking. This is probably due to the short distance between the 2,6-ndc linkers of *ca.* 330 pm only in the calculated “closed” structure. Note that this distance is close to the interlayer distance of 335 pm found in graphite. In summary, molecular dynamics simulations are capable of predicting gating behavior, provided that van der Waals interactions within the DUT-8(Ni) host lattice are explicitly included in the calculations,³⁹ in full agreement with previous calculations on MIL-53.^{49,54-57} This emphasizes the importance of van der Waals interactions for the characteristic adsorption-induced breathing transitions observed in various MOF compounds. It should be noted that the exchange of Ni by Cu, Zn, or Co completely changes the switching behavior of DUT-8²⁷ which illustrates that the type of metal center is also of crucial significance for the breathing transitions.

As mentioned above, MIL-53 is another flexible MOF. In contrast to DUT-8(Ni), the breathing transitions of MIL-53 are less pronounced and do not result in a totally closed structure. Instead, MIL-53 switches between a large-pore and a narrow-pore state depending on the external parameters such as temperature and pressure.⁵³ At xenon pressures below 0.4 bar, MIL-53(Al) prefers its large-pore state beyond room temperature. Decreasing the temperature causes a phase transition to the narrow-pore state. Below a certain threshold temperature, however, MIL-53(Al) transforms back into the large-pore phase. In contrast, the large-pore state is always present at high pressures, *i.e.*, beyond *ca.* 1.5 bar. These phase transitions could be visualized by ¹²⁹Xe NMR spectroscopy using hyperpolarized xenon.³⁸ In the

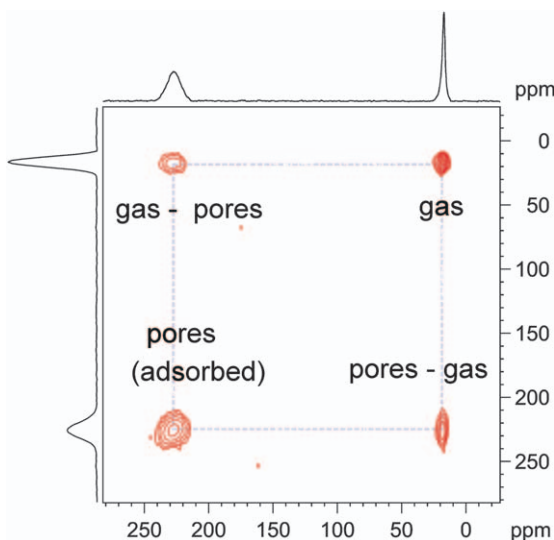


Figure 12.7 2D ^{129}Xe EXSY NMR spectrum measured at 237° K and 15 bar with a mixing time of 25 ms. The presence of cross-peaks indicates exchange between Xe@DUT-8(Ni) and the gas phase. Reproduced from ref. 39 with permission from the American Chemical Society.

case of MIL-53(Al), the changing pore volume and geometry give rise to corresponding changes of the isotropic chemical shift and of the chemical shift anisotropy of the ^{129}Xe NMR signals. As expected, the narrow-pore state exhibits a significantly larger ^{129}Xe NMR isotropic chemical shift and chemical shift anisotropy than the large-pore state.

Figure 12.7 exhibits the two-dimensional (2D) ^{129}Xe EXSY (exchange spectroscopy) spectrum using a mixing time of 25 ms. This experiment demonstrates the high mobility of the xenon atoms between the tunnels of DUT-8(Ni) and the xenon gas phase surrounding the DUT-8(Ni) crystallites. Obviously, the exchange occurs on a time scale of tens of milliseconds, which is indicated by the appearance of well-known cross-peaks between the ^{129}Xe NMR signal of the gas phase and the ^{129}Xe @DUT-8(Ni) NMR signal. This high mobility agrees well with values observed in other MOFs.⁵⁸

In summary, it can be stated that ^{129}Xe NMR spectroscopy significantly contributes to characterizing the pore systems of MOF compounds. It is, furthermore, helpful to understand the breathing/gating behavior of flexible MOFs.

12.5 Conclusions

^{129}Xe NMR spectroscopy is well suited for the study of MOFs. Adsorbed in non-flexible MOFs, xenon exhibits an analogous behavior as observed previously for other non-flexible porous materials such as zeolites. However,

special effects can be observed in the case of flexible frameworks (gate pressure MOFs). These compounds are capable of switching between a closed or narrow-pore state and a large pore state depending on the temperature and pressure. The pores become suddenly filled completely during pore opening. Moreover, the gate pressure MOFs exhibit a pronounced hysteresis, *i.e.*, the gate closing pressure is lower than the gate opening pressure. ^{129}Xe NMR spectroscopy at variable pressure and temperature considerably contributes to the understanding of these interesting effects.

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CHAPTER 13

Hyperpolarized Xenon Biosensors and HyperCEST

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13.1 Using Xenon NMR for Sensing

The isotope ^{129}Xe has a spin 1/2 nucleus, which is good for high resolution xenon NMR, with an abundance of about 24%. The first xenon NMR study in a biological context surveyed the chemical shift of xenon in different environments,¹ including when associated with proteins and membranes. The high polarizability of xenon leads to large changes in chemical shift for different environments. A more detailed study of xenon binding to myoglobin and hemoglobin was done that included determination of binding constants and kinetics.² With these proteins, and many others since, xenon exchange between protein-bound and free in-solution states is in or near the fast exchange limit, so binding interactions are manifested as changes in the xenon shift and linewidth.

Experiments probing protein interactions, particularly at fairly low protein concentrations, were greatly facilitated by use of hyperpolarized xenon.^{3,4} Interest in exploiting xenon as a sensor arose from studies of maltose binding protein (MBP), which has a xenon binding cavity that changes affinity when maltose binds.^{5,6} As maltose is added to a solution of xenon and MBP the occupancy of the binding pocket changes, altering the xenon

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

shift, which thus acts as a reporter of the amount of maltose present. The protein's specificity for binding its natural ligand allows the assay to function in a complex mixture such as cell lysate.⁶ The first examples of using xenon chemical shift as a reporter exploited proteins with natural xenon binding pockets (which are fairly common), but it was also shown that 'reporter' cavities could be engineered into proteins.⁷ The association of xenon with the protein causes broadening as well as the shift of interest. The difficulty in measuring small shifts of broadened lines limits the concentration of analyte detectable with this method to about the micromolar concentration range.

Since the detection sensitivity for hyperpolarized xenon is very high it was realized that if a signal could be generated in slow exchange with 'bulk' dissolved xenon that reported on the presence of an analyte, a better detection limit might be achieved. Fortunately chemists working on host-guest systems had already discovered that cryptophane cages⁸ (Figure 13.1) bind xenon strongly, and that exchange between bound and free xenon was sufficiently slow to give well separated xenon signals in organic solvents. The first cryptophane based biosensors⁹ had a cryptophane-A cage (Figure 13.2) modified for covalent attachment to solubilizing and binding elements. The concept was that when the binding element associated with a protein, a sufficient change in the environment or conformation of the cage would occur such that the chemical shift of xenon would change, thus reporting the binding event. A peptide and biotin were chosen as the solubilizing and binding elements for convenience of synthesis and high binding affinity. As conceived in the design, a significant shift was observed for xenon in the cryptophane when biotin bound to avidin, and the relative intensities of 'caged' xenon signals reflected the molar ratio of the sensor construct to avidin present; the xenon signal then acted as a quantitative sensor for avidin.⁹ Surprisingly the chemical shift of the xenon is so sensitive to the environment that the signals for the enantiomers of the sensor were resolved

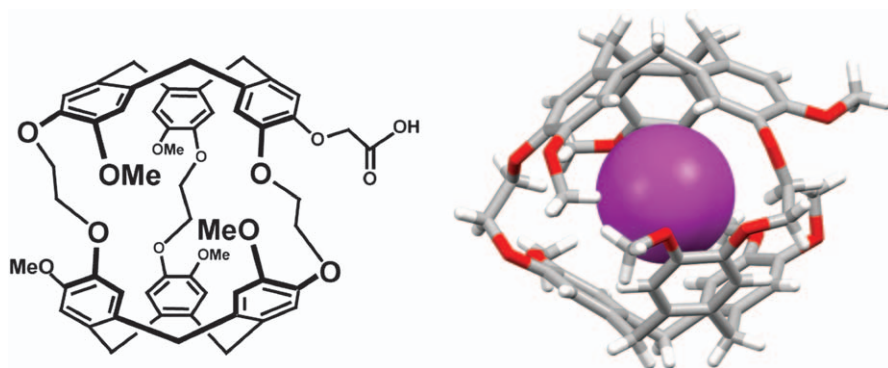


Figure 13.1 A schematic drawing of cryptophane-A monoacetic acid (left), and a stick representation of cryptophane-A with xenon bound (from Cambridge Crystallographic Database, file OJITOR.cif).

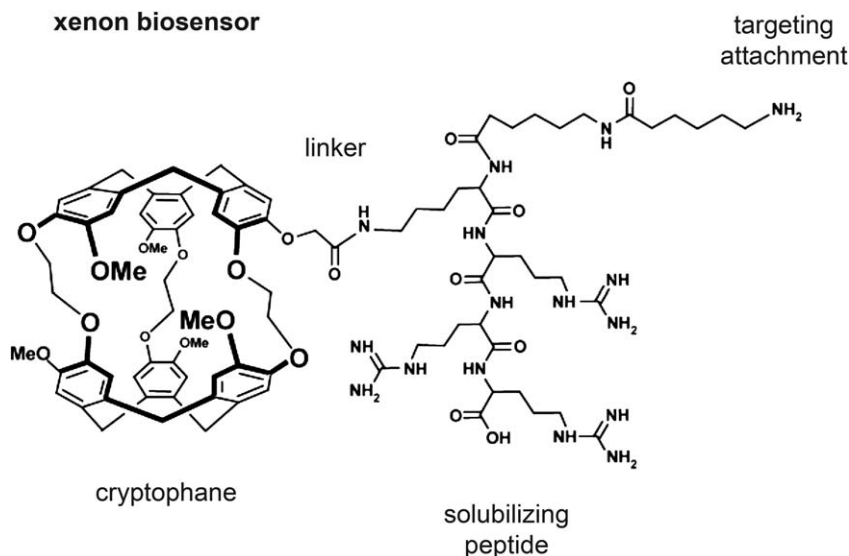


Figure 13.2 A drawing of a xenon biosensor, with a cryptophane-A cage, a linker, solubilizing amino acids and attachment point for the targeting element.

due to interactions with the bound chiral peptide and racemic linker. This experiment established the feasibility of using ‘caged’ xenon, in slow exchange with other dissolved xenon, as a reporter for the presence of a target molecule. Variations on this construct were made to explore the effects of linker length, finding that a moderate length giving considerable flexibility but holding the cage and binding element in proximity is optimum to give reasonably narrow lines while retaining the change in shift induced by binding.¹⁰ Quite a number of variations on this theme, from several labs, have followed and will be discussed below.

13.2 Enhanced Detection

The hyperpolarization of xenon makes it possible to observe signals from low concentrations of biosensors, enabling detection of submicromolar concentrations by judicious signal acquisition.^{11,12} Studies of cryptophane-A associated xenon showed that while the signal is in the slow exchange limit, there is some broadening of the bound xenon due to its relatively short lifetime. In organic solvents the exchange rate is higher, which leads to more broadening of the cryptophane bound xenon resonance. In water the binding of xenon is somewhat stronger, and at ambient temperature the lifetime is about 25 ms, corresponding to a linewidth of ≈ 13 Hz. When the concentration of biosensor is low compared to dissolved xenon (usually the case in a sensing application), the dissolved xenon can act as a polarization reservoir if just magnetization from the caged xenon is excited

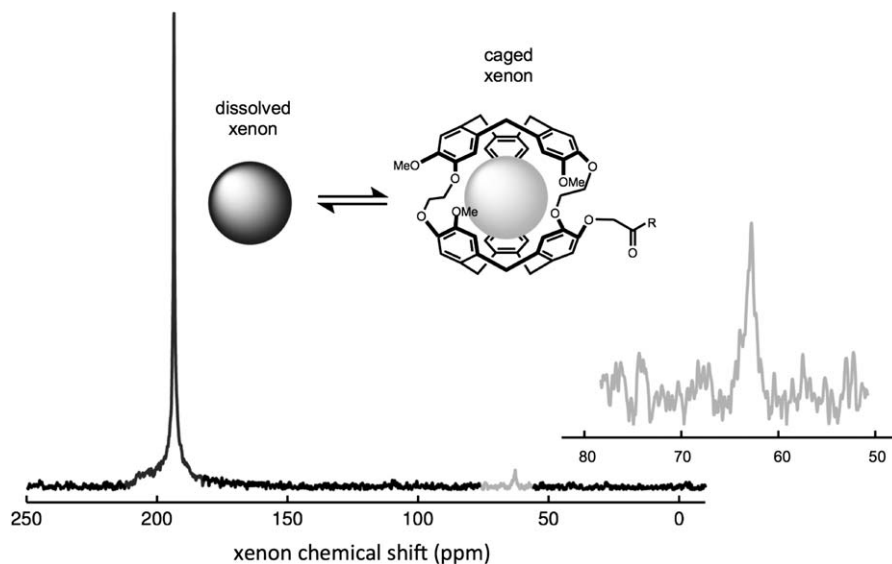


Figure 13.3 A hyperpolarized ^{129}Xe NMR spectrum taken from a solution of a cryptophane biosensor in water. The water dissolved xenon resonance is at about 192 ppm, while the cryptophane associated xenon is at about 62 ppm (shown enlarged in the inset).

(done with judiciously chosen selective pulses since the resonances are well separated, see Figure 13.3).¹¹ With a delay of 100 ms between excitation pulses there is essentially full recovery of the caged xenon magnetization, and many acquisitions can be done before the pool of hyperpolarized xenon is depleted and must be refreshed. This rapid, direct excitation approach allows detection down to the hundreds of nanomolar concentration range with natural abundance xenon and a polarization of a few percent (^{129}Xe enrichment and higher polarization could yield an ≈ 40 fold lower detection limit).

The exchange of xenon between cage and solvent leads to saturation transfer, a reduction of the free xenon resonance when the cryptophane bound xenon resonance is saturated (Figure 13.4). The saturation effects can be large given the relatively long xenon T_1 relaxation times for the unbound xenon relative to the exchange rate. Detection of the presence of the cage can be done by comparing the solvent xenon resonance with and without saturation at the caged xenon frequency. A lifetime of xenon in the cage of 25 ms means that on average 40 xenon atoms pass through the cage per second. If all of these are saturated (the limit of strong irradiation at the cage frequency) for a period of 10 seconds this leads to about 400 xenon atoms saturated per cage, and hence the difference in the solvent xenon signal will be proportionately larger than the directly detected caged xenon signal. The sensitivity gain depends on the exact parameters used for data collection, but can be the order of 40 fold relative to direct detection

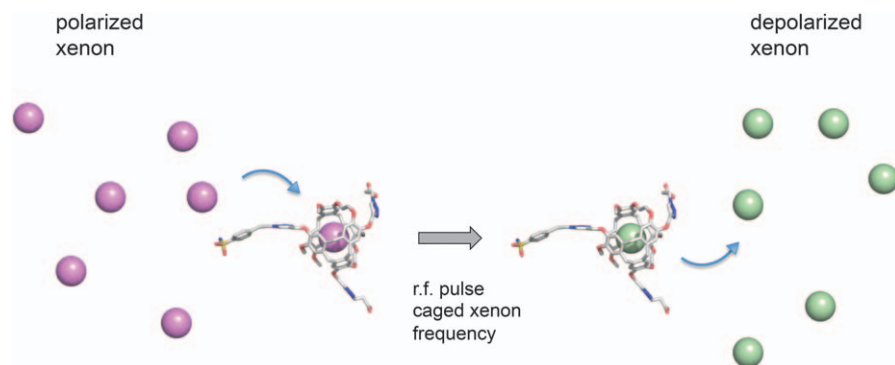


Figure 13.4 Schematic drawing of the hyper-CEST effect in which polarized xenon (left) binds to the cage, where it is saturated by a selective radio frequency pulse, and then is released depolarized (right). The degree of depletion depends on the exchange rate with the cage, the length of the saturation period with the pulse on, and the strength of the pulse.

with rapid acquisition. This approach has been termed hyper-CEST to reflect the reliance on the initial hyperpolarized xenon signal, which is modulated by the chemical exchange saturation transfer (CEST) effect.

13.3 Immobilization of Biosensors for Imaging

The modular construction of xenon cage biosensors allows chemical linkage of the cages to almost arbitrary targeting agents, from small ligands through antibodies and aptamers. While the initial experiments were done using a chemical shift change to detect a binding event, it was soon realized that the selective binding of cages could be used to detect immobile, spatially localized targets with xenon MRI. Such experiments can be done in a manner quite analogous to a fluorescence labeling experiment, introducing the biosensor (with the cage on a sufficiently long tether to provide mobility and a narrow line), allowing binding, washing to remove unbound species, then introducing xenon and detecting the presence of the cage either directly¹³ or with hyperCEST.¹⁴ The first experiments detected biosensors on agarose beads at $\approx 80 \mu\text{M}$ concentration with direct detection, and subsequently at $\approx 5 \mu\text{M}$ with hyper-CEST (Figure 13.5). With optimized biosensors, higher xenon polarization and more efficient imaging sequences much higher sensitivity can be achieved.^{15,16}

13.4 Optimization and Pushing the Detection Limits

Variation of the linker between the cage and targeting agent was mentioned above in the context of minimizing broadening while retaining a chemical shift response to the binding event. Empirically it is found that moderate length linkers with some flexibility work well. Calculations of xenon shifts have indicated that interactions of the cage with protein that transiently

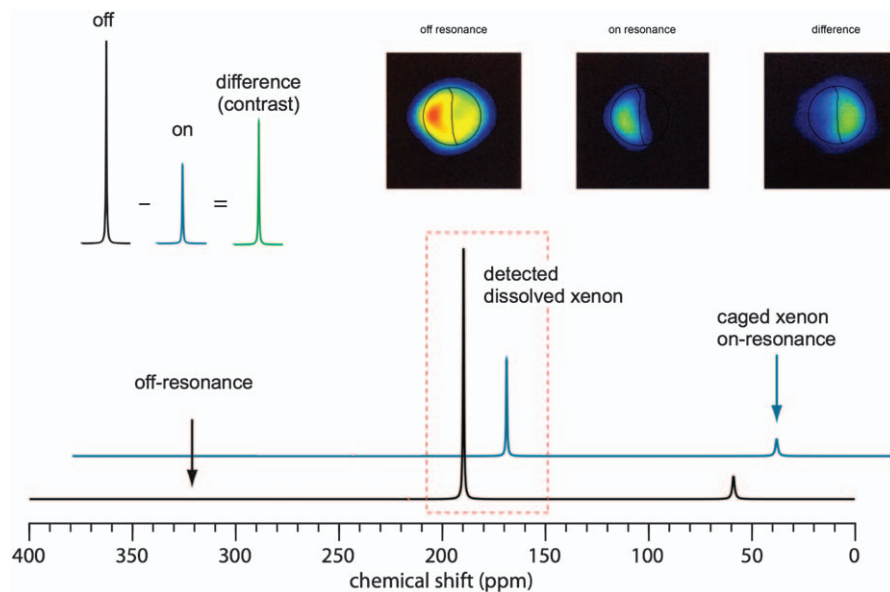


Figure 13.5 Representation of the hyper-CEST effect for imaging. Images are collected after introducing hyperpolarized xenon, one with off-resonance irradiation and a second with irradiation at the caged xenon frequency. The difference shows regions where the on-resonance saturation had an effect due to the presence of the cage. The images at the top right are from a 1 cm diameter tube with a plastic partition in the center. The left portion was loaded with agarose beads with no cryptophane biosensor, the right portion had agarose beads to which cryptophane biosensor was bound. The difference image on the right shows the region containing biosensor.

perturb the structure are responsible for the induced shifts,¹⁷ but it is difficult to intuitively predict or understand the effects of particular cage-linker-target combinations on shifts. A crystal structure of a derivatized cryptophane-A cage linked to a benzenesulfonamide carbonic anhydrase II inhibitor (that shows a substantial shift upon binding) gave a direct view of a successful design (Figure 13.6).¹⁸

The binding of xenon to cages is another area in which there has been biosensor optimization. The saturation transfer rate in hyperCEST is affected both by the occupancy of the cage and the rate of exchange of xenon between cage and solvent. Both of these parameters are complex functions of the molecular structure, and can not presently be independently optimized. However, in the process of making various derivatized cryptophane-A structures it has been found that attachment of pendant groups can make binding tighter, and yet also increase the rate of exchange – making them significantly better hyperCEST agents.²⁵ The cage itself has also been varied by altering the lengths of the linkers between the aromatic caps. Cryptophane-A (with three O-CH₂-CH₂-O linkers, designated [222],

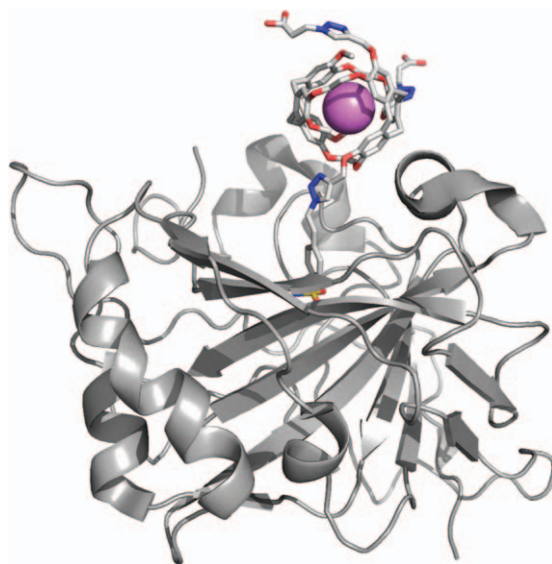


Figure 13.6 The crystal structure of one conformation of carbonic anhydrase II with an inhibitor tethered cryptophane biosensor and xenon bound.¹⁸ Contacts between the cryptophane and the protein lead to a change in chemical shift of the bound xenon. From PDB entry 3CYU.

see Figure 13.1) has a cavity somewhat larger than a xenon atom. The number of methylene groups has been altered, both increasing ([223], [2,3,3] and [3,3,3] = cryptophane E), which leads to weakened binding relative to [222],¹⁹ and also decreasing ([221], [211] and [111]),^{20–22} but exchange kinetics have not been fully explored. The saturation transfer effects can be quantitatively predicted from the Bloch equations (which has been done both analytically²³ and numerically²⁴). It is also worth noting that the exchange of xenon in and out of the cage has a substantial activation energy, and hence the rate is quite temperature sensitive. Triacetic acid cryptophane-A has an exchange rate of 500 s^{-1} at $37\text{ }^{\circ}\text{C}$, giving a very high CEST efficiency, and hence leads to the ability to detect very low concentrations of cages (into the pM range).²⁵

For increasing sensitivity of detection, when localization is the goal rather than detection of binding through induced shift changes, multiple cages have been tethered to each targeting element. The first example of this was just to bind multiple cages in a dendrimer²⁶ with one targeting element attachment point, leading to a few fold increase in signal. Since the cages are not covalently linked they can leach out from the polymer. Better results have been achieved by covalently tethering many cages to a framework, such as a viral coat shell or intact virus. Targeting elements, such as antibodies or aptamers, can also be attached using different conjugation chemistry, or they can be ‘built in’ to the biological assembly. With the spherical MS2 viral coat protein shell ≈ 125 cages could be attached,²⁷ and with a filamentous

phage ≈ 1000 cages per virus can be linked²⁸ (addition of short PEG polymers as well helps prevent aggregation of the derivatized phage). With the double amplification of many cages per target, and many xenons per cage *via* hyperCEST, picomolar concentrations of target can be detected.

13.5 Applications of Xenon Biosensors

As noted above, the first xenon biosensor had biotin attached to enable detection of avidin.^{9,29} Since that time there have been numerous variations described. One of the first of these also introduced the idea of detecting a chemical modification, reported by the xenon. In this example the cryptophane cage was linked to a substrate peptide for a matrix metalloprotease (MMP), using convenient ‘click’ chemistry. It was then shown that cleavage of the peptide by the MMP shifted the resonance of the attached caged xenon.³⁰ In another example cryptophane-A cages were attached to a single stranded DNA oligomer (linked at the 5′ end of the strand with a hexyl chain). The caged xenon resonance shifts by about 2 ppm in the presence of a complementary DNA strand, but not one which is non-complementary.³¹ Even larger shifts were seen when cryptophane was linked to a *p*-benzene-sulfonamide, which is a potent inhibitor of carbonic anhydrase (CA), see Figure 13.6. When the sensor construct bound to the CA-II isozyme, shifts of up to about 6 ppm in the caged xenon spectrum were observed.¹⁸ Shifts were also seen upon binding of a major histocompatibility complex protein to a target peptide carrying a linked cryptophane.³²

Sensors with peptides attached to cryptophane-A have also been studied in the presence of cells,³³ demonstrating that these biosensors were not significantly toxic. Both a very basic peptide and one containing integrin binding RGD repeats, with a fluorescent label, were shown to be taken up by the cells.³³ Transferrin, with cryptophane cages conjugated to lysines, was also shown to be taken up into human erythroleukemic cells, which have abundant transferrin receptor,³⁴ detected both by fluorescence and xenon NMR. Direct xenon interactions with cells (without cryptophane) were also characterized.³⁵ The binding and/or uptake of cryptophanes has been used to selectively detect cancer cells,³⁶ and also to track a population of labeled cells³⁷ using direct detection of bound xenon, and also hyperCEST. Other applications of caged xenon, such as analysis of membrane fluidity³⁸ and indirect detection of analytes,³⁹ have also appeared recently.

13.6 Continued Sensor Development and Further Optimization

The development of new conjugation reactions for coupling biomolecules of interest is an active field, and can help facilitate coupling of cryptophanes to various targeting agents to make new biosensors. “Click” reactions have been applied,^{30,40} but many other reactions are also feasible. Also of significant interest are improvements of binding affinity and

xenon exchange properties of the cages. Altering the linkages between cyclotrimeratrylene caps of the cryptophane has improved performance as a sensor,^{20,21,41} as have changes replacing the aryl methoxy groups with other functionality.^{25,42} Improved syntheses of cages⁴³ should also be helpful in facilitating exploration of new sensors. Some of the new cryptophane variants have xenon binding constants and exchange rates that are near optimal for use with hyperCEST detection (allowing very low concentrations to be detected).^{25,42}

The initial development used cryptophane cages because they had been shown to bind xenon in organic solvents with an exchange rate that would enable loading with hyperpolarized xenon, and cryptophanes provided a natural attachment point for linking to a targeting element. However, it seems likely that other 'cages' should also be useful for biosensors. Xenon dissolves in lipid⁴⁴ and fluorocarbon droplets,⁴⁵ and gives distinct signals. It should be possible to derivatize and target such droplets, though direct detection of binding through induced shifts seems unlikely with these. Other frameworks developed for binding targets (part of a large host-guest chemistry effort over many years) do bind xenon but many are soluble only in organic solvents and do not have good exchange characteristics. Two exceptions are a cucurbit[6]uril derivative (the derivitization helping water solubility),⁴⁶ which binds xenon with affinity comparable to cryptophane and shows slow exchange, and pillar[5]arene⁴⁷ derivatives that show a slow-exchange xenon signal when an alkane is also bound. It seems likely that these and other known 'host' molecules can be modified to be effective for biosensor construction.

The parameters needed for achieving the highest detection sensitivity for a hyperpolarized-xenon based biosensor are context dependent. This is in part due to the requirement for selective saturation of the caged xenon signal without perturbation of the bulk dissolved xenon pool, and also contributions of xenon relaxation through interactions with the surroundings that occur in addition to those with the biosensor itself. Higher exchange rates mean faster saturation transfer but also then more power for complete saturation and less selectivity. The Bloch equation based analyses capture these effects,^{23,24} but require information that is experiment specific and not always known in advance (such as an inhomogeneous contribution to the linewidth). The fractional saturation of the xenon pool in hyperCEST, which is functionally the contrast achieved, depends critically on the concentration of biosensor relative to xenon, the exchange rate of xenon, and the saturation time and xenon T_1 . The sensitivity of the detected xenon signal depends on the initial polarization, rate of xenon delivery to and clearance from the region of interest, and determining its steady state concentration and relaxation rate. Xenon delivery *in vivo* has been explored in animals and humans.⁴⁸ Many anatomical regions develop sufficient xenon concentration to be imaged using xenon MRI. However the signals are fairly weak, so high contrast will be required for reliable biosensor detection *in vivo*. Better delivery of highly polarized xenon will help, but this is

independent of the biosensor. Sources of possible improvement by modifying the biosensors include increasing the binding affinity of xenon to maximize the caged xenon signal being saturated, and further optimization of the exchange rate (to the extent that these can be independently manipulated).

Since xenon cages with different structures give rise to distinct chemical shifts, it is possible to do multiplexed detection of biosensors.^{9,29} Though the basic approach has been described and demonstrated,^{37,49,50} merging multiplexing with hyperCEST will require different optimization than detection of a single species because of the need for selectivity in saturation. From the underlying principles such multiplexing should be possible while still achieving good detection sensitivity.

Acknowledgements

The development of xenon biosensing at Berkeley was a joint undertaking with my teacher, collaborator and friend Prof. Alex Pines and his lab members, who were already experts in applications of hyperpolarized xenon when this effort started. Many students and postdocs in both labs (identified in many of the papers cited here) contributed to the initial ideas and work at Berkeley, for which I am extremely grateful. They are largely responsible for the success of this endeavor. Recent efforts have also benefited greatly from interactions with Prof. Matt Francis and his lab to employ more sophisticated bioconjugation methods for targeting biosensors.

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Biosensing and Study of Biological Cells using Hyperpolarized ^{129}Xe

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14.1 Introduction

Among the species in which nuclear spin can be transiently polarized, xenon has a special place for the study of biological processes due to its physical properties. It has no toxicity, it can be easily handled due to a freezing point at 162 K. Importantly, its large electron cloud gives this atom specific chemical affinities, and a large variability of its NMR parameters: the chemical shift of the monoatomic species has been shown to span a range from 0 ppm (gas phase) to 300 ppm (solid phase¹), longitudinal relaxation time values range from *ca.* 5 seconds (xenon in blood²) to several hours. Its solubility in many biological fluids (a few mM per atm in water at room temperature, hundreds of mM in lipids) makes it a powerful spy of biological events.

In the aim of characterizing biological environments and events, xenon can be used alone, or functionalized by dedicated molecular systems for which it has a high affinity. These systems bear ligands that enable active targeting of biological receptors. This chapter aims at summarizing some of

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

the recent research and development we have developed using free hyperpolarized xenon and xenon in molecular hosts to image or characterize biological cell receptors.

14.2 Hyperpolarized Xenon and Biological Cells

The first experiments dealing with hyperpolarized xenon and biological cells were performed in 1995 by Albert *et al.*² They showed that xenon in the presence of red blood cells (RBC) gave rise to two signals on the NMR spectrum (one assigned to xenon in the plasma and the other one to xenon in RBC) exhibiting different longitudinal relaxation times. Bifone *et al.*³ attributed the 20–24 ppm chemical shift difference between the two signals to the interaction between xenon and hemoglobin present in the intracellular compartment of RBC, the paramagnetism of this protein being in large part responsible for the chemical shift variation. The variation of the chemical shift difference and relaxation time was later correlated to the oxygenation level of hemoglobin.⁴

Recently, prokaryotic, eukaryotic cells, mammalian, vegetal, and yeast cells were studied in the presence of hyperpolarized xenon (Figure 14.1), and the presence of two signals on the ^{129}Xe NMR spectrum could be systematically observed, even in the absence of a known paramagnetic system: one signal at lower magnetic field corresponding to xenon in the intracellular compartment and the second one to xenon in the bulk.⁵ This means that xenon crosses the plasma membrane while keeping its polarization and that the exchange rate between both compartments is lower than the frequency difference between both environments. Recently it has thus been pointed out that each cell type has its own signature on the ^{129}Xe NMR spectrum. As expected, the area of the signal of xenon in the inner compartment is directly proportional to the number of cells, and the presence of a mixture of cells can straightforwardly be detected, as well as the cell uptake of toxics.

But undoubtedly the most important point is that the presence of distinct signals for the inner compartment and the bulk enables measurement of the xenon in–out exchange rate with simple ^{129}Xe NMR experiments. This gives direct access to parameters usually difficult to obtain: the fluidity and permeability of the cell membrane.

We used this property for different applications, among which the most striking was the recognition of cells resistant to chemotherapy.⁶

Most of the chemotherapeutic agents are small hydrophobic molecules that cross the cell membrane in a passive (energy-free) way based on a concentration gradient. But some cells, have developed a membrane transporter system, notably *via* p-glycoprotein (Pgp),⁷ in order to favor expelling of the cytotoxic drugs to the external medium. Whereas cell permeability to water is now well measured and understood, few methods are proposed to evaluate cell permeability to hydrophobic drugs.⁸ The *in vitro* techniques used so far are, for example, based on the detection of the internalization of small hydrophobic fluorophores such as rhodamine 123,⁹ and PCR

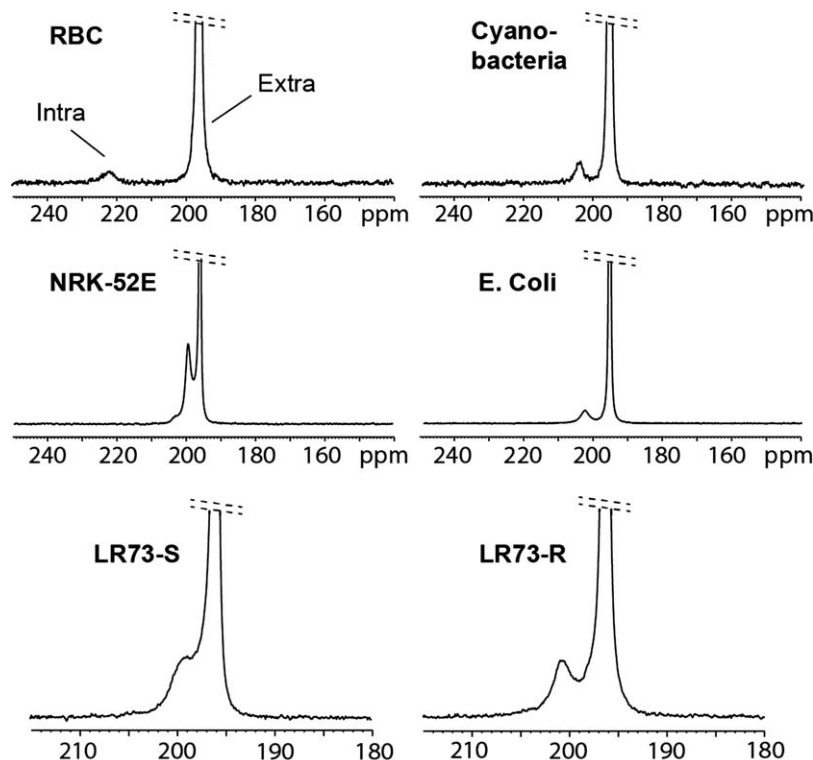


Figure 14.1 ^{129}Xe NMR spectra obtained for suspensions of different living cell types. The samples contained red blood cells, *Synechocystis* cyanobacteria, NRK-52E renal proximal cells, *Escherichia coli* TOP10 bacteria and Chinese Hamster Ovary LR73 cell lines (left: sensitive to chemotherapy; right: resistant to chemotherapy. See text).

methods¹⁰ which witness the presence and activity of p-glycoprotein. These techniques are slow as they require an incubation delay. There is thus a real need for fast evaluation of cell permeability.

In our proof-of-concept, two Chinese Hamster Ovary cell lines were used: the wild type (LR73-S) sensitive to chemotherapeutic drugs, and the multi-drug resistant type derived from it (LR73-R). This system had already been used several times as a model for studying cell drug resistance *via* Fourier transform infrared spectroscopy¹¹ and fluorescence correlation spectroscopy.¹² While after trypsination, classical optical microscopy did not allow us to discriminate LR73-S and LR73-R cells from their size or aspect, their one-scan ^{129}Xe NMR spectra recorded in the same conditions (same temperature, same amount of xenon and number of cells) revealed two immediate differences (Figure 14.1): (i) for the same number of cells, the ratios R between the signal areas of the inner and outer compartments differed by a factor 3.3 (see Table 14.1); the number of xenon atoms internalized per cell was in our experimental conditions more than three times

Table 14.1 Results of the ^{129}Xe NMR experiments in terms of chemical shift difference, integral ratio (cell/bulk) R and xenon in- and out-exchange rates for four different cell samples.

Sample ^a	δ splitting ^b (ppm)	Integral ratio R (cell/bulk) ^b	$k_{\text{out}}/\text{s}^{-1}$	$k_{\text{in}}/\text{s}^{-1}$
LR73-S	3.00 ± 0.21	0.561 ± 0.022	29.4 ± 5.7	16.5 ± 3.8
LR73-R	4.46 ± 0.05	0.167 ± 0.066	86.5 ± 16.7	14.4 ± 6.3
LR73-S + CsA ^c	3.00 ± 0.10	0.168 ± 0.024	32.2 ± 27.6	5.4 ± 2.3
LR73-R + CsA ^c	2.70 ± 0.04	0.113 ± 0.038	28.9 ± 7.8	3.2 ± 2.8

^aThe data of the first two rows were obtained with 10^8 cells, those of rows 3 and 4 with 4×10^7 cells (explaining the differences in R value).

^bThe measures were performed on 5 different replicate samples. The error corresponds to standard deviation. The signals in the high field regions of the ^{129}Xe spectra were fitted by Lorentzians. After all these experiments, it was checked by colorimetric trypan blue exclusion test that the cells were still alive.

^cCsA: cyclosporin-A.

more elevated in the sensitive cell line than in the resistant cell line; (ii) the chemical shift difference significantly varied between the two cell lines: the inner xenon signal for the resistant cell line was low-field shifted by about 1.5 ppm with respect to the signal from sensitive cells. The observed chemical shift variation can be explained by the difference of plasma membrane structure, due to the over-expression of p-glycoprotein, which organizes its own micro-environment.¹³

However as variation of the xenon chemical shift could also be due to the presence of toxics or of other paramagnetic proteins, we undertook the measurement of a third parameter: the xenon exchange rate across the cell membrane. This was performed *via* a simple 1D NMR experiment consisting of selective inversion of the xenon signal in the cell and acquisition after a variable delay (Figure 14.2).

The last two columns of Table 14.1 give the exchange rates of xenon in and out of the cells. The xenon *out* rate was three times more elevated for the resistant cell line than for the sensitive cell line, whereas the *in* rates were similar. It is worth mentioning that in principle there is no direct correlation between xenon *out* rate and drug resistance, as the noble gas has no role in the cell metabolism. But xenon seems to be assimilated to a small hydrophobic molecule, recognized as such by the cells and thus behaves similarly as some anticancer drugs or antibiotics with respect to trans-membrane exchange mechanisms. An elevated xenon efflux rate thus seems to be the signature of the mechanism of active elimination of cytotoxic molecules at the origin of resistance to drugs. Such a marked difference in xenon-*out* rate could be explained by a pronounced action of p-glycoprotein, and anyway represents a very efficient way to discriminate resistant and sensitive cell lines.

In order to assess the validity of our interpretation, the effect of cyclosporine-A (CsA), a revertant agent was tested. CsA is known to interact with p-glycoprotein and to block its action. The same ^{129}Xe NMR experiments were performed in two other cell samples of LR73-S and LR73-R

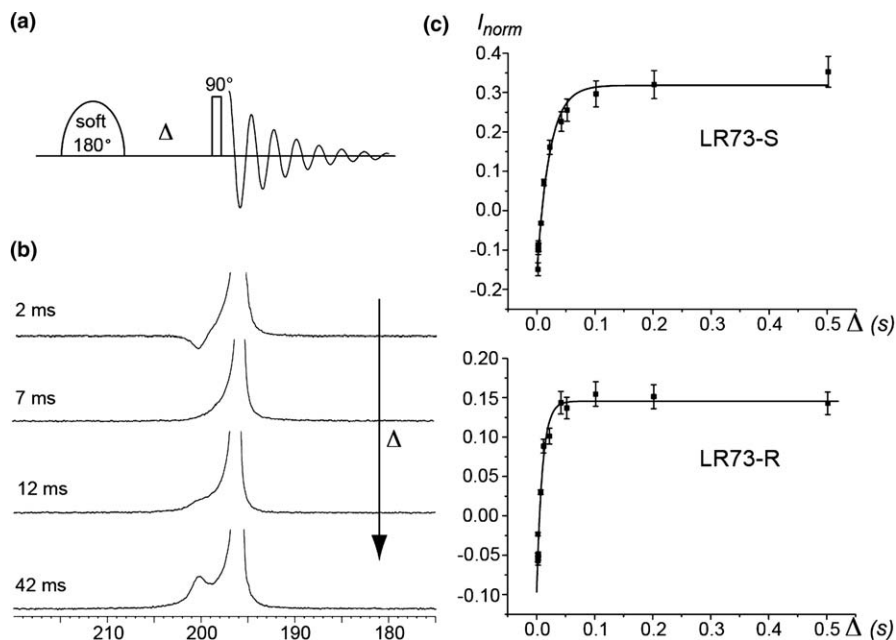


Figure 14.2 Measurement of the xenon in-out exchange rates. (a) NMR sequence. (b) Hyperpolarized ^{129}Xe NMR spectra obtained for various delays Δ on a sample of LR73-R cells. (c) Result of the exchange experiment: normalized area of the intra-cell signal as a function of Δ for LR73-S and LR73-R cell lines. The curves represent the best fit to the theoretical equation $A - B \exp(-k\Delta)$, where $k = k_{\text{in}} + k_{\text{out}}$. For extracting k_{in} and k_{out} , we used $R = k_{\text{in}}/k_{\text{out}}$.

cell lines incubated with cyclosporine-A. The ^{129}Xe NMR parameters for the LR73-S cells were not significantly affected by the incubation. But remarkably the characteristics of the spectrum of the LR73-R sample were now close to these of the sensitive cell sample: smaller chemical shift difference, higher number of internalized xenon atoms per cell and xenon out rate lower than without cyclosporine-A (compare lines 2 and 4 of Table 14.1). This experiment was repeated several times with different cell concentrations (from 10 to 150 million in 530 μL solution), and gave similar results. Obviously the higher xenon *out* rate for cells resistant to chemotherapy combined with a constant – but cell concentration dependent for a given quantity of noble gas – xenon *in* rate led to a lower ratio R between the signal areas of the inner and outer compartments.

As far as we know, no other NMR method exists for the determination of the permeability of the cell membrane to hydrophobic molecules. The proposed method is quick and straightforward, and does not require the use of a model. It only needs a high field NMR spectrometer or imager equipped with a standard probe and hyperpolarized xenon. The *in vivo* extension can be envisioned in localized spectroscopy. On a dense tumor, spatial selection

of a region where a given cell line predominates should enable its analysis via the ^{129}Xe NMR spectrum.

14.3 Xenon in Functionalized Host Systems

Using hyperpolarized xenon alone as a sensor for biological cells requires, however, a homogeneous magnetic field. Except for some cells, such as RBCs or cyanobacteria, the low frequency difference between the signals of xenon in the bulk and in the cell compartment should not enable direct *in vivo* use. Furthermore, even if the previous paragraph and very recent developments show that a significant contrast can be observed on endogenous xenon host systems such as cells, gas vesicles¹⁴ and spores,¹⁵ where there is a large number of low-to-intermediate affinity sites, to date none of these systems is able to target specific biological receptors. Therefore, several molecular systems for which xenon develops a particular affinity and that give the noble gas a specific resonance frequency well resolved from the bulk signal, have been chemically decorated with biological ligands: microporous nanoparticles,¹⁶ cage-molecules^{17–20} and capsids.^{21,22} The important parameters are the ‘in’ resonance frequency (that must be very different from the frequency of the bulk signal), the in–out xenon exchange (that must be slower than this frequency difference but fast enough to enable further gain in sensitivity), and the xenon binding constant (a high affinity is useful when the xenon/host concentration ratio is low).

Most of the biological sites/receptors and mechanisms that have been targeted so far after the proof-of-concept made on the avidin–biotin system²³ are enzymes^{24,25} and cell-surface receptors.^{26–28} The reason lies in the necessity to increase the local density of xenon hosts, using the catalytic cycle in the first case or the possible high number of receptors per cell and cell-internalization in the second case.

A biosensor proposed by Dmochowski *et al.* was based on a cryptophane-A linked to a RGD peptide.^{29,30} The interaction of the biosensor with integrin induced a variation of the caged xenon frequency. Fluorescence of a Cy3 label showed internalization of the construct, but no ^{129}Xe spectrum of the biosensor in the cell was presented.

The spatial resolution obtained in classical MRI is not sufficient to enable distinction between the intra-cellular compartment and the bulk in ^{129}Xe MRI experiments. Therefore, in order to prove that targeting of cell-surface receptors was achieved, bimodal (fluorescence– ^{129}Xe NMR) biosensors were conceived. Our group chose the transferrin system,²⁸ responsible for the transport of iron to cells, for several reasons. (i) Transferrin receptors are cell surface receptors which are internalized when transferrin is recognized. (ii) Some cells such as K562 erythroleukaemic cells exhibit a high number of receptors (more than 10^5). (iii) Labeling transferrin, an 80 kDa protein, by a small molecule (the cryptophane) is not expected to modify drastically the biological activity. (iv) The affinity of holo-transferrin for the receptor is 700 times higher than that of apo-transferrin, and obviously the presence of

the strongly paramagnetic Fe^{3+} ions could lead to fast xenon relaxation and could affect the sensitivity of the technique. But in case of a too drastic relaxation, iron ions could have been replaced by indium ions. (v) In our approach a cryptophane bearing an activated ester was synthesized. This enabled a non-specific (statistical) grafting of the cryptophane on some lysine residues of the protein (Figure 14.3a). Thus, various biosensors are easily built *via* this method.

Fluorescence microscopy showed the internalization of the biosensor in K562 cells (Figure 14.3b). After proper washing designed to separate the cells from the supernatant, the hyperpolarized ^{129}Xe NMR spectra were recorded.

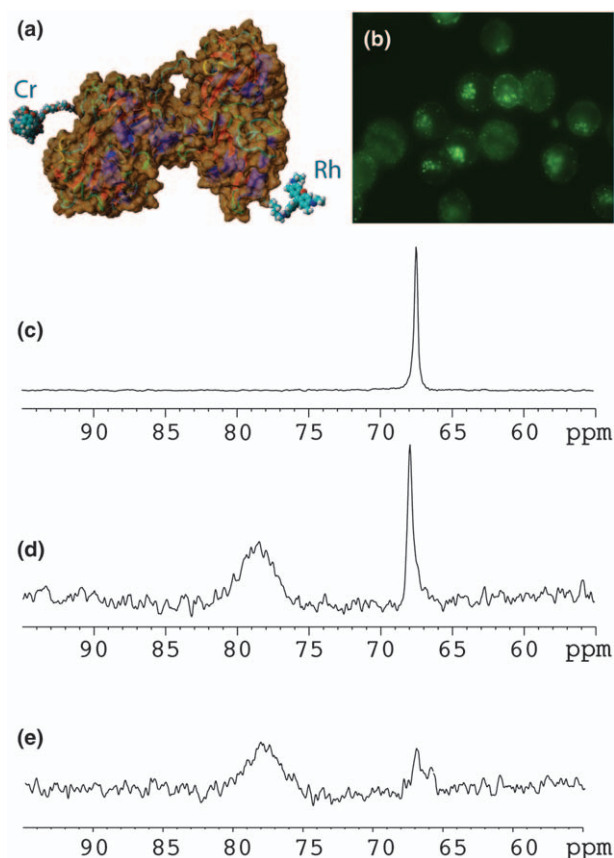


Figure 14.3 Cell internalization of a ^{129}Xe NMR-based biosensor. (a) Structure of the transferrin biosensor, where some cryptophane (Cr) and Rhodamine Green (Rh) moieties are non-specifically grafted on the Lys residues of the protein. (b) Fluorescence microscopy image of K562 cells incubated with this biosensor. (c)–(e) High field region of the ^{129}Xe spectra of (c) the transferrin biosensor in the supernatant, (d) the transferrin biosensor in the cell suspensions, (e) the BSA biosensor in the cell suspensions. Adapted from ref. 28.

The spectrum of the cell part is characterized by the presence of two signals at high field, separated by 10 ppm (Figure 14.3d). The first one (at 68 ppm) has the same chemical shift as the biosensor in the supernatant and the second peak represents the biosensor in the cell membrane. This indicates the internalization process of the transferrin biosensor even if the hydrophobicity of cryptophane induces a non-specific interaction of the probe with the plasma membrane of the cells. For comparison, a construct based on bovine serum albumin (BSA) was also designed. This protein was known to give rise to non-specific interactions with cells. After washing, the ^{129}Xe NMR spectrum of the cell part displayed the same signals but with a lower overall intensity and a ratio largely in favor of the membrane location (Figure 14.3e). This is in agreement with the fact that such a construct is internalized *via* pinocytosis.³¹ This leads to the conclusion that although the transferrin biosensor is recognized and internalized by the cells, a part of the interaction occurs with the cell membrane, undoubtedly due to the hydrophobic character of the cryptophane.

Note that Klippel *et al.* recently used such a non-specific interaction of hydrophobic cryptophane moieties with the plasma membrane to perform MRI using the contrast between xenon in the free cage and xenon in the cage in interaction with the membranes for the purpose of cell-labeling.³² Palaniappan *et al.* designed a biosensor where many cryptophanes are grafted on a bacteriophage expressing antibodies against EGFR (Epithelium Growth Factor Receptor).²⁶ They revealed, *via* HyperCEST, the specific interaction between the biosensor and the cell surface receptors.

14.4 Optimized Detection

The exchange of xenon between different environments, each having its own ^{129}Xe NMR spectral signature, is the advantage of the use of hyperpolarized xenon. It enables replenishment of the hyperpolarization after it has been destroyed by rf excitation or irradiation. Thus two methods can be used to detect the small reservoir constituted by xenon in cell (Xe@cell) or in a biosensor (Xe@host): directly with a series of soft pulses at the small reservoir frequency,³³ each followed by detection, or indirectly *via* detection of the variation of the bulk xenon signal after irradiation at the small reservoir frequency (HyperCEST³⁴). The latter method has the advantage of being more sensitive, but the transient character of the hyperpolarization requires a continuous and homogeneous supply of polarized gas. Indeed except using normalization protocols, the lowest detectable amount of xenon in its host system or in the cell cannot be lower than the fluctuation level of supplied xenon magnetization.

As a way-around, we extended to xenon a method recently proposed to provide in one or two scans the whole Z-spectrum.³⁵ A field gradient applied during the rf irradiation enables saturation of the small reservoir in a region of the NMR tube. Detection performed in the presence of a second field gradient decodes to give the Z-spectrum (Figure 14.4).^{36,37}

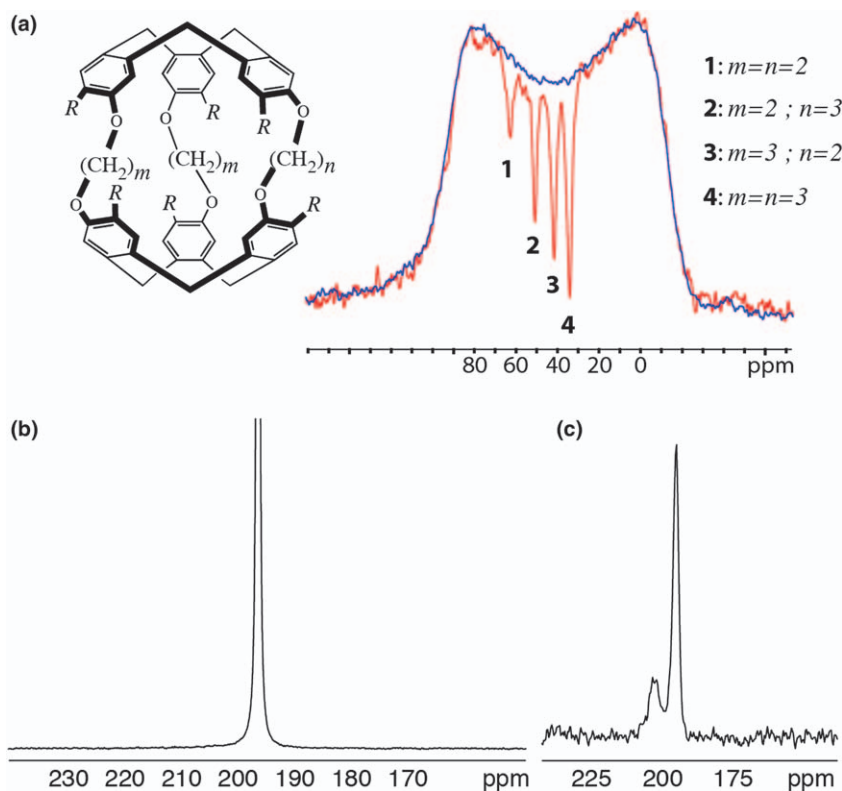


Figure 14.4 ^{129}Xe Ultrafast Z-spectroscopy. (a) Mixture of hexacarboxylated cryptophanes at $6\ \mu\text{M}$ each, with CW saturation during $7.5\ \text{s}$ at $2.4\ \mu\text{T}$ (red) and without saturation (blue). (b)–(c) Sample of 25 million *S. cerevisiae* in $1.6\ \text{mL}$ H_2O (estimated volume fraction 0.17%). (b) One-scan ^{129}Xe NMR spectrum; (c) Two-scan UFZ spectrum ($8\ \text{s}$, $B_1^{\text{sat}} = 2.4\ \mu\text{T}$).

Therefore, reliable results can be obtained even with significantly fluctuating xenon magnetization between pulses, and averaging can now be performed on a spectrum-by-spectrum basis (adding several UFZ-spectra to increase the signal-to-noise ratio). The robustness of UFZ toward magnetic field inhomogeneity is a further advantage of the approach.

14.5 Concluding Remarks

These few examples reveal how hyperpolarized xenon can be a potent probe of intra-cellular processes. In our laboratory these research efforts will be continued by (i) still reducing the number of cells needed for detection with help of micro-fluidics and micro-detection, (ii) developing the concept of a 'smart' probe, where a signal transduction inside the cell induces a xenon frequency shift. Several issues remain unresolved: what is the bio-distribution of xenon inside the cells that gives rise to such chemical shift

variations? Is it possible to transfer the xenon polarization to some metabolites in the cells? There is no doubt that future years will see a keen interest in the use of polarized xenon for the study of biological cells.

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Cryptophane-Based ^{129}Xe NMR Biosensors

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15.1 Introduction

The intrinsic NMR chemical shift sensitivity, exceptional signal-to-noise, and chemical inertness of hyperpolarized xenon-129 (HP ^{129}Xe) make it attractive for many magnetic resonance applications and a natural complement to proton magnetic resonance imaging (MRI). For imaging studies, ^{129}Xe is a viable alternative to ^3He , which is rare and nonrenewable; moreover, among the noble gases, ^{129}Xe (with 54 electrons) possesses unique capabilities for host-guest chemistry based on its volume ($\sim 42 \text{ \AA}^3$), significant polarizability (which yields high affinity for void spaces and good water solubility),¹ and lack of radioactivity. Pioneering biological imaging studies with HP ^{129}Xe targeted the pulmonary void spaces in mouse lungs.² There have since been many additional xenon studies in the lungs, brain, and other tissues in both mouse and human.^{3–7} These applications are enhanced by recent improvements in spin-exchange optical pumping methods that yield near unity ^{129}Xe hyperpolarization.⁸ These successes motivate greater use of HP ^{129}Xe in human imaging, with the caveat that xenon is limited to areas where the gas will readily diffuse, after inhalation or direct injection. While the $\sim 13 \text{ s}$

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

T_1 of HP ^{129}Xe in oxygenated blood is sufficiently long on the MRI time-scale for brain diffusion, the T_1 of HP ^{129}Xe in breast tissue can be increased to 23–29 s through an intravenous co-injection of a lipophilic solution.^{9,10} Although very soluble in organic solvents and lipid environments, xenon exhibits low affinity for endogenous proteins and other biomolecules; attempts to engineer high-affinity xenon-binding sites into proteins have thus far been unsuccessful.¹¹ Thus, xenon should not localize to biomolecular targets *in vitro* or *in vivo*, unless biosensors with high xenon affinity are employed. Here, we summarize lessons learned over the past decade as we have worked to develop cryptophane-based HP ^{129}Xe NMR biosensors for biological imaging applications.

15.2 Cryptophane Synthesis

Most xenon biosensors developed to date employ an organic host molecule with a hydrophobic cavity that can reversibly bind xenon in aqueous solution. Host candidates with modest room-temperature xenon association constants include: hemicarcerand ($K_A \approx 200 \text{ M}^{-1}$), α -cyclodextrin ($K_A \approx 20 \text{ M}^{-1}$), and calix[4]arene derivatives ($K_A \approx 14 \text{ M}^{-1}$).^{12–14} These affinities are on par with xenon–protein association constants (the highest being myoglobin at 200 M^{-1}),¹⁵ which has limited their utility for most applications. Water-soluble cucurbit[6]uril has significantly higher xenon affinity ($K_A \approx 3000 \text{ M}^{-1}$) but presents synthetic challenges to achieve single-site functionalization for biomolecular targeting.¹⁶ The most studied xenon-binding molecule is cryptophane-A (Figure 15.1, $R = \text{CH}_3$), where two cyclotriguiacylene caps are tethered by three ethylene linkers. The linker length of various cryptophanes is denoted numerically, where cryptophane-A is a variety of cryptophane-222.¹⁷ Cryptophane-A was first synthesized in 1981 but it was not until 1998 that it was determined to have a room-temperature xenon association constant of 3000 M^{-1} in a non-competing

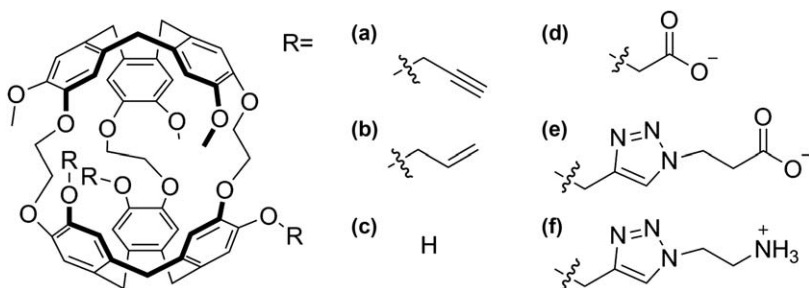


Figure 15.1 Cyclotriguiacylene units tethered by three ethylene linkers with various R groups named. (a) Tripropargyl cryptophane; (b) triallyl cryptophane; (c) trihydroxy cryptophane; (d) triacetic acid cryptophane-A (TAAC); (e) tris-(triazole propionic acid) cryptophane (TTPC); (f) tris-(triazole ethylamine) cryptophane (TEC).

organic solvent, $\text{C}_2\text{D}_2\text{Cl}_4$.^{17,18} Notably, C_3 -symmetric cryptophane-A is chiral, but is usually isolated and used as the racemic mixture of stereoisomers.

The design of xenon-binding molecules is informed by the work of Mecozzi and Rebek, who tabulated the known host–guest interactions dominated by dispersion forces and determined that a guest-to-host volume ratio of 0.55 ± 0.09 optimally balances favorable van der Waals (enthalpic) contributions with the entropic cost of host crowding.¹⁹ [Notably, this empirical formula was not derived for host–guest interactions in water, where the hydrophobic effect yields favorable entropic contributions.] Indeed, in work using hexa-carboxylic acid cryptophane-A derivatives in D_2O , it was shown that increasing the size of the cryptophane cavity, going from two-carbon linkers to three-carbon linkers, decreased the xenon association constant ($K_A \approx 6800 \text{ M}^{-1}$ for cryptophane-222 and $K_A \approx 1000 \text{ M}^{-1}$ for cryptophane-333) in addition to shifting the Xe@cryptophane peak 30 ppm upfield.^{20,21} Conversely, decreasing the cage internal volume using one-carbon (*i.e.*, methylene) linkers, increased the room-temp association constant to $10\,000 \text{ M}^{-1}$.²² These cryptophane derivatives have promising features for use as xenon biosensors, including high xenon affinity and ease of manipulating ^{129}Xe NMR chemical shift through cage design.

A limitation of cryptophane host molecules is their poor water solubility. In 2007, we published a templated, 10-step synthesis for a water-soluble tri-functionalized cryptophane *via* tripropargyl cryptophane and a subsequent Cu(I)-catalyzed [3 + 2] azide-alkyne cycloaddition (CuAAC) with azido-propionic acid (**1e**).²³ The resulting compound termed tris-(triazole propionic acid)cryptophane (TTPC) had a room-temperature xenon association constant of $17\,300 \text{ M}^{-1}$ in water, significantly higher than previously published cryptophane derivatives (Table 15.1).^{20,23} We postulated that desolvation of xenon in water entropically drives cryptophane binding. In order to investigate how the solubilizing linkers affect xenon binding, we synthesized in 13 steps a triacetic acid cryptophane-A derivative or TAAC (**1d**), with the carboxylates $\sim 5 \text{ \AA}$ nearer to the cavity.²⁴ Interestingly, TAAC exhibited a marked increase in xenon binding affinity (Table 15.1). To investigate how the charge on the solubilizing groups affects xenon binding, we synthesized a tris-(triazole ethylamine)cryptophane (TTEC), following the same protocols as TTPC, while conjugating 3-azidoethylamine in the last step.²⁵ As shown in Table 15.1, the amine groups afforded a cryptophane host with nearly 1.3-fold improved xenon affinity, producing the highest known xenon affinity for any host molecule. For all three water-soluble cryptophanes, the Gibbs free energy had

Table 15.1 Thermodynamic parameters for xenon binding to water-soluble derivatives of cryptophane-A. Measured by ITC in buffer at pH 7.0 and 293 K.

Cryptophane	$K_A (\text{M}^{-1} \times 10^4)$	$\Delta G (\text{kcal mol}^{-1})$	$\Delta H (\text{kcal mol}^{-1})$	$T\Delta S (\text{kcal mol}^{-1})$
TAAC	3.33 ± 0.28	-6.06	-4.34 ± 0.66	1.72
TTPC	1.70 ± 0.17	-5.69	-3.14 ± 0.20	2.55
TTEC	4.20 ± 0.20	-6.20	-3.58 ± 0.93	2.62

very similar enthalpic and entropic components (Table 15.1). The favorable entropy term likely results from the dissolution of the clathrate shell surrounding xenon in water along with the release of water molecules from the cryptophane cavity. A key feature of this system is the use of three solubilizing moieties, which helps to keep the cryptophane in an open, xenon-accessible state, known as the crown-crown conformation. It has been shown previously that the cryptophane can also adopt a crown-saddle or ‘imploded’ conformation in the absence of a guest molecule.^{24,26,27} Furthermore, the types of solubilizing moiety and their distance from the cryptophane interior are postulated to modulate the number of waters binding inside the cavity, which compete with xenon binding.²⁷

In 2011, we reported a shorter six-step synthesis of **1a** and **1b** with an improved yield of 6%.²⁸ This built on the work of Brotin *et al.* who reported a milder $\text{Sc}(\text{OTf})_3$ cyclization for cyclotriguacylene formation, removing the need for low concentrations and protection/deprotection steps.²⁹ The use of either tripropargyl cryptophane (**1a**) with CuAAC or trihydroxy cryptophane (**1c**) with amide coupling (following acetate addition) affords a facile means of functionalizing the cage with solubilizing or targeting moieties. It is notable that the tri-functionalized cryptophanes TTPC, TAAC, and TTEC show similar water solubility to the reported hexa-functionalized cryptophanes and exhibit significantly better xenon-binding affinities. We postulate this is a result of cation chelation by the six carboxylates, which may block xenon entry and also stabilize water inside the cavity. The cryptophane work performed to date has yielded a ~ 300 ppm chemical shift window for encapsulated xenon in water (by modulating the cage volume or appending ruthenium) as well as tens of micromolar xenon dissociation constants.^{22,25,30,31}

15.3 Cryptophane Characterization

Methods for measuring xenon binding parameters to host molecules have been refined in recent years. Early work used either changes in ^1H NMR chemical shifts upon ^{129}Xe binding or integration of bound and free ^{129}Xe resonances to calculate the binding affinity of cryptophane.²³ These methods, however, suffer from large errors.²⁰ To develop a more sensitive method for measuring xenon binding affinity for water-soluble cryptophane, we took advantage of xenon’s ability to quench fluorescence of organic chromophores by the heavy atom effect.³² This was previously shown by very efficient Xe quenching of pyrene bound to apomyoglobin.³³ Using $15\ \mu\text{M}$ TTPC (**1e**), experiments were conducted at 293 K in 1 mM phosphate buffer at pH 7.2 by titrating a solution of 1 atm-saturated (5.05 mM) aqueous xenon. Fluorescence maximum intensity *vs.* xenon concentration (0–5.05 mM) data were fitted to a single-site binding model:

$$\frac{[\text{Xe @ } \mathbf{1e}]}{[\text{Xe}] + [\mathbf{1e}]} = \frac{[\text{Xe}]}{[\text{Xe}] + K_D} \quad (15.1)$$

We also demonstrated the utility of isothermal titration calorimetry (ITC) for measuring xenon–cryptophane association constants, which gives data in excellent agreement with the fluorescence quenching method.^{23,24} ITC has the advantage of providing both enthalpic and entropic xenon-binding parameters for a single cryptophane concentration, but requires significantly more cryptophane sample, particularly as the enthalpic contribution to xenon–cryptophane binding is only a few kcal per mole.

We further investigated the interactions between cryptophane and guest molecules by X-ray crystallography. Cryptophane is known to encapsulate a large size range of guests from methane (28 Å³) to chloroform (72 Å³), and these guests bind with similar affinity ($K_A \approx 130\text{--}230\text{ M}^{-1}$).^{19,34} In an effort to explain why xenon binds with so much higher affinity, we co-crystallized cryptophane-A, **1a**, and **1b** with methanol, xenon, and chloroform and found that the cavity internal volume (80–102 Å³) varied with guest size.²⁷ Importantly, it was observed that in the xenon-bound structure, van der Waals interactions were nearly optimized, with an interior cavity volume of 85–89 Å³ and guest: host volume ratio of 0.47–0.49.

15.4 Biosensors

In developing the first xenon biosensor, Pines, Schultz, and coworkers elegantly showed how to functionalize the cryptophane to achieve the dual aims of targeting streptavidin and improving water solubility.³⁵ In cryptophane-A one methoxy group was replaced with a free hydroxyl group which was then converted to a carboxylic acid. Coupling of the carboxylic acid with the amino-terminus of a protected peptide on resin and subsequent coupling with a biotin linker afforded a water-soluble, targeted biosensor. Avidin binding generated a ~ 2.3 ppm chemical shift change for HP ¹²⁹Xe encapsulated in the biotin-conjugated biosensor.³⁵ In a follow-up study, one resonance was observed for mono-allyl-substituted cryptophane-A.²¹ However, upon conjugating the cryptophane with a chiral CKR peptide two peaks appeared, 0.15 ppm apart. These peaks were attributed to the RL and LL diastereomers. After the cryptophane was further derivatized with the biotin linker through maleimide chemistry a new racemic chiral center was formed, generating RLR, RLL, LLR, and LLL combinations for which four “bound” peaks were assigned.²¹ The observed sensitivity of xenon to diastereomerism is problematic for many biosensing applications, as it “dilutes” the xenon-biomarker signal, and complicates peak assignments as well as efforts to selectively irradiate ¹²⁹Xe in a specific environment, as required for many NMR experiments.

Following up on this research, our laboratory demonstrated the ability of HP ¹²⁹Xe to report on an enzyme cleavage event by appending racemic cryptophane with a peptide substrate for matrix metalloproteinase-7, a known cancer biomarker. The ¹²⁹Xe NMR spectra showed two peaks before cleavage and two new peaks after cleavage <1 ppm upfield of the original peaks.³⁶ Because the xenon signal was effectively split between the

diastereomers, the next work, by Dutasta, Berthault, and others, utilized enantiopure cryptophane-A that was grafted with a 20-mer oligonucleotide.³⁷ ^{129}Xe NMR spectra were measured for the biosensor alone, the biosensor with a complementary DNA strand, and biosensor with non-complementary DNA strand. The biosensor plus complementary strand was shifted 1.5 ppm upfield of the other two samples, and all three samples exhibited one bound peak, as expected for single enantiomers.³⁷ Surprisingly, however, when the concentration was increased from micromolar to millimolar levels, both the biosensor alone and the biosensor plus noncomplementary strand were seen to foam and exhibit multiple Xe@biosensor peaks. It was hypothesized that this was the result of increased microemulsions and micelle/vesicle formation.³⁷ This observation highlights the importance of developing highly water-soluble xenon biosensors.

A subsequent work appended cryptophane-A with a peptide ligand to major histocompatibility complex (MHC). Specifically, Schlundt *et al.* used the hemagglutinin (HA) peptide which binds human leukocyte antigen (HLA) DR1. The design employed a solubilizing linker, which acted as a ~ 35 Å spacer between the cryptophane and the peptide binding moiety.³⁸ The ^{129}Xe NMR spectrum revealed one peak for the bound and unbound biosensor, with a $\Delta\delta$ of only 1 ppm.³⁸ While the spacer improved solubility, it positioned the xenon too far from the peptide.

Heretofore, targeted xenon biosensors were mono-functionalized derivatives of cryptophane-A, but our work with water-soluble TAAC, TTPC, and TTEC suggested that we could achieve both better xenon binding and simplified ^{129}Xe NMR spectra with a tri-functionalized cryptophane. Building on earlier work in our laboratory using mono-functionalized cryptophane with a linear (RGD)₄ repeat,³⁹ we functionalized tripropargyl cryptophane (**1e**) with a cyclic peptide RGDyK, known to have high affinity and specificity for $\alpha_v\beta_3$ integrin, and two 3-azidopropionic acids with CuAAC.⁴⁰ Interestingly, despite the cryptophane chirality and potential for diastereomerism, we observed only one ^{129}Xe @biosensor NMR peak when the biosensor bound to $\alpha_v\beta_3$ integrin, and it was 4.1 ppm downfield from the free biosensor. This taught us that by using a well-solubilized cryptophane, it is possible to engage protein targets using short tethers and still obtain well-resolved ^{129}Xe NMR spectra. These data and unpublished results from our laboratory suggest that improving biosensor solubility in water can decrease Xe sensitivity to diastereomers. However, this hypothesis requires further testing.

In order to investigate the cell compatibility of xenon biosensors we fluorescently labeled our cRGDyK-cryptophane and performed cell uptake, viability and specificity studies. The MTT assay demonstrated $\geq 60\%$ viability at 75 μM biosensor for three cell lines. Confocal microscopy studies with the cancer cell line, AsPC-1, and normal human fibroblasts, HFL-1, showed preferential biosensor uptake in AsPC-1 and further demonstrated that uptake could be blocked with antibody or excess cRGDyK peptide (Figure 15.2a and b). Flow cytometry confirmed 2–3-fold greater uptake over

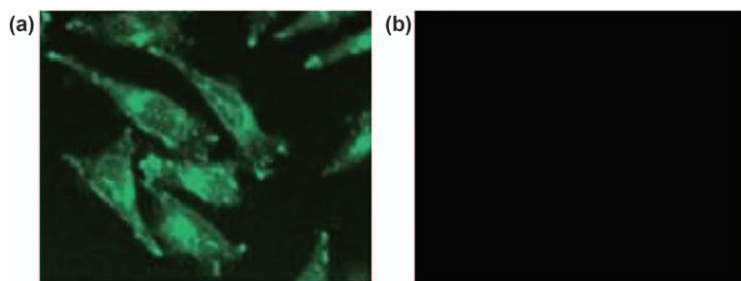


Figure 15.2 Cellular uptake studies using confocal microscopy. 1 μM Alexa Fluor 488-labeled c[RGDyK]-cryptophane targeting AsPC-1 cells (a) after 1 h incubation and (b) with blocking co-treatment of 0.15 mg mL^{-1} anti- α_v antibody. Adapted from ref. 37.

antibody and cRGDyK blocked cells and 4-fold greater uptake in AsPC-1 *vs.* HFL-1.⁴⁰ Our studies also demonstrated targeting of $\alpha_v\beta_3$ integrin and $\alpha_{\text{IIb}}\beta_3$ integrin with nanomolar affinity and specificity and low cytotoxicity at concentrations required for NMR experiments. This work paved the way for cellular NMR spectroscopy and imaging experiments, which are now underway in several laboratories.^{41,42}

15.4.1 Biosensor Design for Multiplexing Applications

Because of the large ^{129}Xe NMR chemical shift window for ^{129}Xe bound to cryptophanes in water, Pines *et al.* postulated in 2001 that HP ^{129}Xe NMR should be amenable to multiplexed detection using a cocktail of cryptophane biosensors.³⁵ One should ideally obtain only one “bound” peak for each biosensor, and these should be well resolved from each other (ideally >5 ppm away) as well as from the “free” biosensor peaks. Already, large chemical shift changes ($\Delta\delta = 7.5$ ppm) upon target complexation have been achieved in our laboratory.⁴³ Additional work is needed to probe how the nature of the xenon biosensor–protein interaction, diastereomerism, and cryptophane solubility affect the ^{129}Xe NMR spectrum.

15.5 Xenon Biosensors Targeting Carbonic Anhydrase

To explore xenon biosensor–protein interactions and other important issues in xenon biosensor design, our laboratory has employed a carbonic anhydrase (CA) model system, which has biomedical relevance for cancer detection.^{44–47} CA is a ubiquitous zinc metalloenzyme that catalyzes a simple but physiologically important reaction: the reversible hydration of carbon dioxide to form bicarbonate and a proton.^{48–50} Five classes of evolutionarily unrelated CA exist (α -, β -, γ -, δ -, and ζ -CAs), with humans expressing fifteen isoforms of α -CA.⁴⁶ All fifteen isozymes share a conserved fold consisting

of a central ten-stranded β -sheet surrounded by helical connections.⁵¹ The catalytic active site of α -CA is positioned at the base of a conical cavity approximately 15 Å wide and 15 Å deep and is comprised of a catalytic Zn^{2+} ion exhibiting tetrahedral coordination with three conserved histidine residues and a hydroxide ion.

Cell-surface biomarkers provide attractive targets for disease detection using xenon biosensors that can remain in the extracellular milieu. Thus, two membrane-bound isoforms of α -CA, CAIX and CAXII, are of particular interest due to their well-documented connection to cancer.^{45,52–57} A common feature of tumors is hypoxia resulting from uncontrolled proliferation of cancer cells away from oxygen-carrying blood vessels.^{53,58,59} Hypoxia regulates the expression of CAIX and CAXII through hypoxia-inducible factor-1 (HIF-1).^{45,52} CAIX and CAXII act to mitigate intratumoral acidosis (a consequence of increased glycolysis rates) by generating bicarbonate that is imported into the cell to act as a buffer.^{52,53} The close association between CAIX/CAXII and hypoxic tumors makes α -CA an attractive target for molecular biosensing. Our group aims to design xenon biosensors that report unique ^{129}Xe NMR chemical shift signatures for CAIX and CAXII that are detectable by MRI/MRS.

CAII, a cytosolic isoform of α -CA, has served as the archetype to guide the development of xenon biosensors in our laboratory. CAII is widely recognized as a model system for rational drug design⁵¹ and, importantly, CAII shares the same overall fold and active-site architecture as the catalytic domains of CAIX and CAXII.^{47,60,61} Benzenesulfonamide was chosen as the affinity tag for our biosensor due to its high affinity for CAII and generally high affinity for other isoforms of α -CA.^{46,62,63} The length of the alkane linker between the benzenesulfonamide and cryptophane moieties was tuned to position the encapsulated xenon close to the protein surface while still allowing for sufficient mobility of the cryptophane. Three racemic biosensors with varying linker lengths were prepared: **C6B**, **C7B**, and **C8B** (Figure 15.3), all incorporating a cryptophane-A derivative decorated with a *p*-benzenesulfonamide affinity tag and two propionic acids to increase water solubility.

The crystal structure of **C8B** bound to wild-type CAII was determined at 1.70 Å resolution by Aaron *et al.* in 2008.⁶⁴ The occupancy of **C8B** was refined to 0.5 (with the $\text{M}_\text{o}\text{M}_\text{o}$ and $\text{P}_\text{o}\text{P}_\text{o}$ enantiomers having occupancies of 0.25, respectively). An encapsulated xenon atom was confirmed by a Bijvoet difference Fourier map calculated from anomalous scattering data and refined with occupancy of 0.5. The overall fold of CAII was largely unperturbed by binding of **C8B**, and only a few conformational changes were observed along the active-site rim. Close examination of the interface between the biosensor and protein revealed only a few cryptophane–protein interactions, suggesting that the cryptophane experiences a high degree of translational and rotational freedom. Such biosensor mobility is advantageous for ^{129}Xe NMR spectroscopy as it yields narrower line widths, thereby increasing the sensitivity of ^{129}Xe NMR measurements in solution.^{64,65}

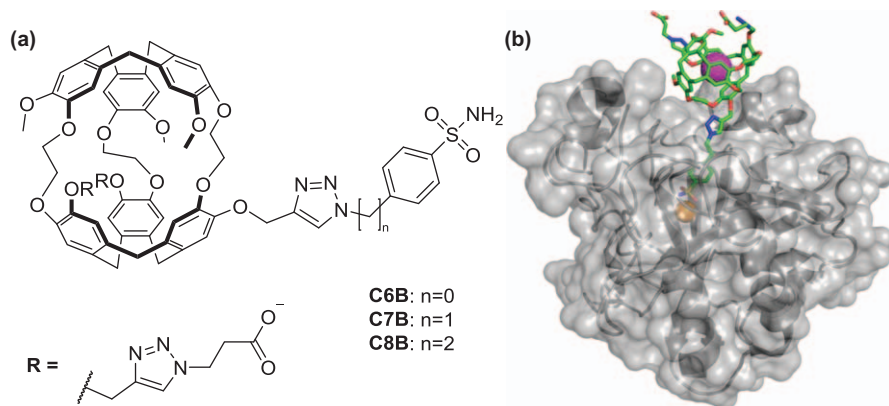


Figure 15.3 Three biosensor constructs incorporating a cryptophane-A derivative labeled with benzenesulfonamide affinity tag and two solubilizing moieties. (a) **C6B**, **C7B**, and **C8B** biosensors. (b) Crystal structure of xenon encapsulated by **C8B** (only the M_oM_o enantiomer is shown for clarity) bound to CAII (PDB ID: 3CYU). The Xe atom is shown in magenta; the active-site Zn²⁺ is orange; **C8B** is shown with carbon (green), oxygen (red), nitrogen (blue), and sulfur (yellow).

Table 15.2 ¹²⁹Xe NMR chemical shifts for **C6B**, **C7B**, and **C8B** in solution, bound to CAI or CAII.

Biosensor	CAI (ppm)		CAI Δ (ppm)	CAII (ppm)		CAII Δ (ppm)
	Unbound	Bound		Unbound	Bound	
C6B	63.7	69.2	5.6	63.1	68.2	5.1
C7B	63.7	66.9	3.2	63.7	71.2, 67.0	7.5, 3.3
C8B	63.3	67.9, 66.3	4.5, 3.0	63.2	68.2, 66.9	5.0, 3.7

Following the determination of the **C8B**-Xe-CAII crystal structure, biosensor binding to CA was further characterized by ¹²⁹Xe NMR spectroscopy and isothermal titration calorimetry (ITC).⁴³ These studies also examined biosensor binding to CAI, a cytosolic isoform of α-CA with high structural similarity to CAII. ITC measurements of biosensor binding to CAI and CAII gave dissociation constants in the 10–100 nM range for all three biosensors. Interestingly, the dissociation constants for the full-length biosensors were comparable to those of the biosensors lacking the cryptophane. These ITC data support the observation made from the crystal structure of **C8B**-Xe-CAII that there are limited interactions between the cryptophane of the bound biosensor and the residues lining the rim of the active-site cavity. Yet, despite this limited interaction, all three biosensors showed distinct and reproducible ¹²⁹Xe NMR chemical shifts upon binding CAI and CAII, respectively (Table 15.2). (The methodology of HP ¹²⁹Xe NMR spectroscopy is described in Section 15.6.) The HP ¹²⁹Xe NMR spectrum of racemic **C7B** bound to CAII is shown as an example (Figure 15.4).

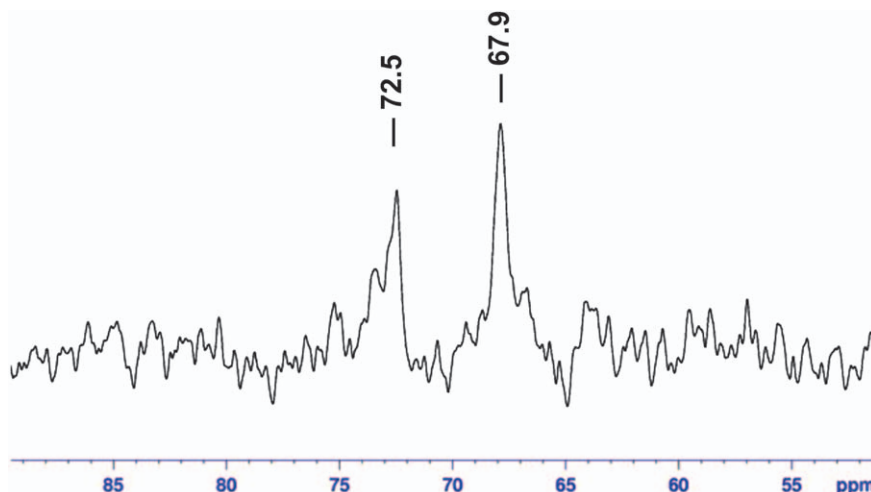


Figure 15.4 Hyperpolarized ^{129}Xe NMR spectrum of racemic **C7B** bound to wild-type CAII, with chemical shifts somewhat dependent on buffer composition, in this case 50 mM Tris- SO_4 (pH 8.0), 10% glycerol. The peaks at 72.5 and 67.9 ppm correspond to ^{129}Xe encapsulated by biosensor bound to CAII. Spectra were averaged over 40 scans and fitted using 30 Hz Lorentzian broadening.

The unique ^{129}Xe NMR chemical shifts for biosensors bound to CAI or CAII demonstrate the potential of xenon biosensors to discriminate between isoforms of α -CA. CAI and CAII are structurally homologous, thus it is expected that xenon tethered in the active-site channel experiences similar steric environments. However, the distribution of hydrophobic and hydrophilic residues lining the active-site channels varies between CAI and CAII; the large electron cloud surrounding the encapsulated xenon nucleus is sensitive to these differences, and thus the two isoforms are distinguishable by HP ^{129}Xe NMR spectroscopy. It is expected that CAIX and CAXII will also report characteristic ^{129}Xe chemical shifts upon binding the xenon biosensor, thereby allowing for the selective detection of these isoforms by MRS/MRI.

Interestingly, racemic **C7B** bound to wild-type CAII reports two ^{129}Xe NMR chemical shifts (Figure 15.4). **C8B** also reports two chemical shifts when bound to CAI and CAII, respectively. It was initially hypothesized that the two observed ^{129}Xe chemical shifts were the result of diastereomerism, with the (+) and (−) enantiomers of **C7B** interacting differently with the chiral active-site channel of CAII.⁶⁶ However, the ^{129}Xe NMR spectra of enantiopure (+) and (−) **C7B** both report two “bound” ^{129}Xe NMR resonances when bound to CAII.⁶⁶ An alternative hypothesis is that **C7B** is binding to CAII at a second ‘b’ site near the protein surface while concurrently binding at the Zn^{2+} active-site. Indeed, crystal structures of CAII bound with benzenesulfonamide inhibitors reveal inhibitor binding at a surface ‘site b’ *via* hydrogen bonds

with Asp-19 and His-15.⁶⁷ The ^{129}Xe NMR spectrum of C8B bound to a CAII mutant with 'site b' disabled (*via* a D19L point mutation) shows only one bound peak (unpublished results). Additional mutagenesis studies are underway to further explore this two-site hypothesis.

Our work with CAII as a model system demonstrates that HP ^{129}Xe NMR spectroscopy used in conjunction with targeted xenon biosensors is a viable technique for the detection of biomolecules of interest. Cryptophane chirality undoubtedly complicates biosensor design, and new synthetic routes to enantiopure cryptophane will be useful for some applications.⁶⁸ However, in several examples investigated in our laboratory, racemic cryptophane can be employed usefully while avoiding the appearance of multiple "bound" peaks, through judicious target selection and consideration of cryptophane solubility. As described in more detail below, HP ^{129}Xe coupled with chemical exchange allows for ultrasensitive (nM-to-pM) biosensor detection. The sensitivity of xenon can distinguish biosensors simultaneously bound to similar targets (*e.g.* isoforms of α -CA). A well-designed biosensor will bind its target in a 1:1 stoichiometric ratio, and report a single characteristic chemical shift that is detectable by MRS/MRI.

15.6 Hyperpolarized ^{129}Xe NMR Spectroscopy

For the many biosensor studies from our laboratory reported in this chapter, HP ^{129}Xe was generated using the spin-exchange optical pumping (SEOP) method⁶⁹ with a home-built ^{129}Xe hyperpolarizer, based on the commercial model IGLXe.2000 by GE. A gas mixture of 89% helium, 10% nitrogen, and 1% natural abundance xenon (Linde Group, NJ) was used as the hyperpolarizer input. A 795 nm circularly polarized diode laser was used for optical pumping of Rb vapor. ^{129}Xe atoms were polarized to 10–15% after cryogenic separation, sublimation, and collection in pressure valve NMR tubes (New Era Enterprises Inc, Vineland, NJ). NMR tubes were vigorously shaken to mix HP ^{129}Xe gas with biosensor solutions before being put into the magnet.

All ^{129}Xe NMR measurements were carried out on a Bruker BioDRX 138 MHz NMR spectrometer (^1H = 500 MHz), using a 10 mm broadband (BBO) NMR probe. Sample temperature was controlled by VT unit on NMR spectrometer to ± 1 K. Eburp1 or Eburp2 shaped pulses were used to selectively excite the Xe@biosensor peak. A delay of 0.15 s was given between scans to allow for fresh HP ^{129}Xe exchange into cryptophane. Spectra were averaged over 10–40 scans. Fourier transformed spectra were processed with zero filling and Lorentzian line-broadening. Spectra were referenced to the shift of xenon gas at 0 ppm when extrapolated to 0 atm.

15.6.1 Exchange Measurements

The exchange rate of xenon between aqueous solution and cryptophane can be readily determined by 1D EXSY NMR, using the same pulse sequence as previously described.²¹ A different exchange delay period τ_{mix} was given

following the initial observation of caged xenon z-magnetization. A second observation of z-magnetization was then made, which gave the exchange-recovered intensity. This magnetization recovery occurs through exchange with polarized xenon in solvent during the mixing period, allowing the normalized intensity to be fitted with a first-order exchange mechanism. Using this method, Xe-TAAC exchange lifetime was determined to be 22 ± 3 ms at 297 K in aqueous solution, which predicts a line width of 14 Hz. This consistent with a NMR peak line width of 27 Hz measured in corresponding experiments.

15.6.2 Hyper-CEST Experiments: Ultrasensitive Detection of TAAC

Development of the hyperpolarized ^{129}Xe chemical exchange saturation transfer (Hyper-CEST) technique has significantly improved biosensor detection sensitivity.^{70,71} The reversible binding of xenon to its host system is exploited by this indirect detection method based on chemical exchange. Our lab has shown a detection limit of water-soluble cryptophane TAAC as low as 1.4 pM (Figure 15.5).⁷² Saturation frequencies of DsnoB-shaped pulses were positioned at 65.8 ppm (194.3 – 128.5 ppm) and 322.8 ppm

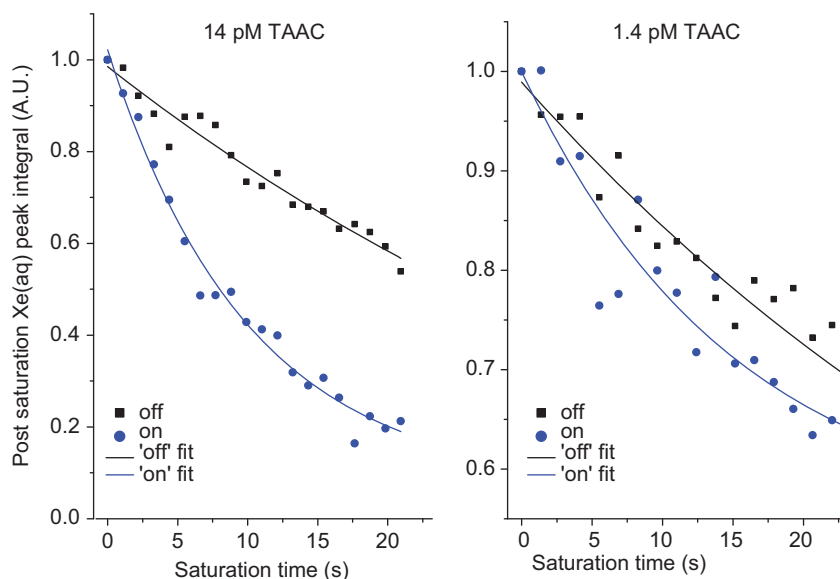


Figure 15.5 ^{129}Xe NMR Hyper-CEST profiles of 14 pM and 1.4 pM TAAC at 320 K plotted as the Xe(aq) peak intensity vs. saturation time. Exponential fits of signal are shown as red and dark curves. In each experiment, the following pulse sequence parameters were used: sp6 (pulse length)=2.6 ms, d12 (delay between pulse)=20 μs , maximum L6 (number of saturation cycles)=8000 for 14 pM and 10 000 for 1.4 pM.

(=194.3 + 128.5 ppm), for “on” and “off” resonance, respectively. The different depolarization rates observed from on- and off-resonance experiments indicated effective saturation transfer caused by chemical exchange.

The observed depolarization in Hyper-CEST experiments arises from both T_1 relaxation and biosensor-mediated saturation transfer, with TAAC and the on-resonance rf pulse acting together as a ‘spin catalyst’. However, after taking into consideration the concentration of xenon and biosensor, the catalyzed xenon depolarization rate (k_{cat}) was more than one order of magnitude faster than the k_{exch} value obtained from 1-D EXSY or NMR line width analysis, which means more efficient relaxation was observed in the Hyper-CEST scheme. Recently, a more quantitative investigation into the Hyper-CEST effect by Zaiss *et al.*⁷³ led to a similar first-order kinetic constant λ_{CEST} as our previously derived k_{cat} , and further suggests that the simple 2-pool exchange system studied in the Bloch-McConnell equations does not fully describe the observed depolarization rate at picomolar TAAC concentration. We propose a possible associative exchange mechanism, where the cryptophane-bound Xe atom undergoes two different exchange pathways, both with solvated HP ^{129}Xe and with a more accessible HP ^{129}Xe cloud surrounding the cryptophane. Additional mechanistic studies are needed to align theory with experiment.

15.7 Future Directions

Future work will aim for better understanding of the depolarization mechanism in the Hyper-CEST process, cellular ^{129}Xe NMR/MRI experiments with our biosensing systems, and advancement of cryptophane and other synthetic host molecules as well as more biological structures for use in ^{129}Xe NMR spectroscopy and particularly Hyper-CEST.

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Caged Xenon in Phospholipid Membrane Environments

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16.1 Introduction

Cellular membranes mediate or govern a large variety of the functions of cells.¹ Biological membranes are mainly composed of different phospholipids, which themselves represent the most common molecules in mammalian tissue after water.² They not only determine the compartmental structure of cells, they also self-assemble into a highly dynamic two-dimensional membrane. The properties of these membranes, such as their overall fluidity or their permeability, are largely determined by the phospholipid composition. Cells can lower the membrane fluidity either by decreasing the ratio of phospholipids with unsaturated fatty acid chains over saturated phospholipids or by increasing the concentration of the sterol cholesterol. A variety of diseases alter the fluidity of the cell's membrane.^{3–6} This makes it an interesting candidate for a biomarker for the detection of different diseases. In this chapter we report on the state of art of how NMR of caged xenon (Xe@host) can be used to obtain information about lipid environments, the membranes' dynamics such as fluidity, and their composition with non-invasive NMR spectroscopy and imaging.

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

16.1.1 General Interaction of Xe and its Host with Biomembranes

Xenon is *ca.* 14 times more soluble in lipid environments than in aqueous solution,⁷ thus Xe atoms tend to partition into biomembranes when being present in aqueous solution. However, the exchange of Xe atoms in and out of the membrane appears fast on the NMR time scale because the associated change in chemical shift for, *e.g.*, micelles in aqueous solution is only *ca.* 1–5 ppm, depending on the lipid concentration.⁸ In most cases, the NMR signal of Xe associated with cells is shifted because of such partitioning into lipid environment (Xe@lipid) and it can only be distinguished from the Xe in aqueous solution (Xe@aq) resonance at reduced temperatures (277 K). An exception are red blood cells in which the presence of the iron-containing heme groups contribute to an additional shift, yielding an overall separation in chemical shift of *ca.* 25 ppm.⁹

The spectral dispersion greatly improves when xenon is encapsulated in cryptophane-A (CrA), a highly hydrophobic (water solubility < 30 μM) supramolecular cage that itself easily partitions into lipid environments⁸ and that serves as a host for Xe atoms.¹⁰ Counterintuitively, the cage around the noble gas makes its NMR signal more sensitive to the molecular environment than is the case for “naked” Xe. The chemical shift difference between the Xe@CrA complex in lipid (Xe@CrA@lipid) and aqueous (Xe@CrA@aq) environments can be as large as 10 ppm. For example, at 296 K the Xe@CrA@lipid resonance is at 70 ppm while the Xe@CrA@aq is at 60 ppm,⁸ with respect to the Xe gas phase signal as a chemical shift reference for 0 ppm. Chemical shifts of Xe@CrA remain more or less unaffected when changing from membrane models^{12,13} to cell suspensions.¹¹

The uptake of both cage and xenon into lipid environments is very efficient and allows for high-sensitivity detection. Investigations at different cage/lipid ratios showed that cage concentrations of 10^{-5} – 10^{-4} M can partition completely into the lipid environment once the lipid fraction in aqueous solution is larger than 0.1. This is derived from the observation that the Xe@CrA@aq resonance vanishes completely for such conditions.⁸ Even with the hydrophilic fluorescent dye DY682 chemically coupled to CrA the ratio CrA@lipid/CrA@aq was of the order of 10^3 as measured with Förster Resonance Energy Transfer (FRET).¹³ This means that more than 99.9% of the overall cages partition into the membrane, thus forming a locally highly concentrated host–guest system with Xe that motivates further investigation by chemical exchange saturation transfer (CEST) methods. Along this line, Xe hosts are currently under investigation as MRI contrast agents, and such high unspecific partitioning of CrA into hydrophobic environments has to be kept in mind. Although this can be of advantage for sensitive membrane detection (see Section 16.1.3), it can mask other interactions such as specific cell targeting mediated *via* molecular recognition (*e.g.*, an antibody coupled to the cage) that has to be more efficient than the lipophilicity of the cage.

Direct detection of Xe@CrA in membrane environments can be challenging since the accelerated exchange in this environment (compared to caged Xe in aqueous environment) causes additional line broadening. However, exactly this exchange behaviour is very favourable for saturation transfer experiments based on the CEST technique. When performed with hyperpolarized nuclei, this approach is called Hyper-CEST.¹⁴ Taking advantage of the great sensitivity of Hyper-CEST enables the detection of small amounts of CrA which is located in lipid environments. The Hyper-CEST response of Xe@CrA@lipid depends on various parameters, including exchange rates, relaxation rates, and CrA and Xe concentrations.¹⁵ This is difficult to study quantitatively under complex conditions of real cell membranes. Artificially prepared membranes are much easier to examine yet are still excellent models of biomembranes,¹⁶ leading to their extensive use. Additionally, membrane models have the advantage that they are for example more robust, better manageable and can be consistently prepared. Their preparation is briefly summarized in the next section.

16.1.2 Preparation of Membrane Models

Homogeneously sized unilamellar membrane models can be obtained either *via* sonication or extrusion.^{17,18} For both methods, the desired membrane components first have to be dissolved in a mixture of chloroform and methanol (molar ratio of 1:1). After complete evaporation of the organic solvents the remaining lipid film on the surface of the glass flask is hydrated with an aqueous buffer, which causes the formation of (multilamellar) vesicles. These come with an undesired complexity as a model system and have to be transformed into unilamellar vesicles. To do so, the vesicle suspension has to be either sonicated or extruded. In sonication based methods, unilamellarity and size distribution are influenced by phospholipid composition and concentration, temperature, sample volume, and sonication time and power. Hence, reproducibility between prepared batches is challenging. A better reproducible size distribution is obtained *via* extrusion by first freeze-thawing the solution followed by pushing the emulsion several times through a filter system which possesses a distinct pore size, for example 100 nm. The stability of the vesicles depends mainly on their composition but also on their diameter. For example, small unilamellar vesicles (diameter < 100 nm) have a high curvature inducing a high surface tension and can spontaneously fuse to larger vesicles during a time range of several days. Experiments should therefore be performed with freshly prepared samples.

16.1.3 Hyper-CEST Imaging of Membrane-Embedded Xe@host

As mentioned above, the highly concentrated host-guest system in lipid environments motivates indirect detection using the Hyper-CEST approach.

Chemical exchange of the Xe atoms into the host is faster in lipid environments than in water which yields a very efficient saturation transfer. Such exchange rates are, however, related to some line broadening that may cause unwanted signal contribution from a neighbouring resonance that is too close in terms of chemical shift (called “spillover effect”). Careful selection of the applied saturation power guarantees sufficient selectivity since the chemical shift difference between the two Hyper-CEST responses of Xe@CrA@aq and Xe@CrA@lipid is *ca.* 10 ppm large. This enables selective Hyper-CEST imaging of the two different environments, as demonstrated by Meldrum *et al.*⁸ In that study the obtained image resolution was 14 mm² using chemical shift imaging (CSI) of 100 μ M CrA with an acquisition time of *ca.* 14 min per data set. Today, improved Xe polarization and optimized image acquisition pulse sequences¹⁹ make it effortless to detect 20 μ M CrA in 500 μ M egg yolk phosphatidylcholine (EYPC) in 600 μ L phosphate buffered saline in a single Hyper-CEST image acquisition in *ca.* 15 s. Figure 16.1 demonstrates this frequency-selective Hyper-CEST imaging with an in-plane resolution of 0.2 mm². Setting the frequency of the saturation pulse to 60 ppm (1a) and dividing the signal by the control signal (obtained with off-resonant saturation (2)), both compartments show a Hyper-CEST effect (3a). However, the CEST effect is less pronounced in the inner compartment which contains EYPC. This can be explained by CrA being embedded into the EYPC membrane and thus being excluded from contributing to the saturation transfer at this frequency. Changing the saturation pulse frequency to 71.5 ppm (1b) only the inner compartment shows a CEST effect (3b), where Xe and CrA can interact within the EYPC membrane. The latter resonance is not detectable in the direct Xe NMR spectrum with 32 acquisitions which again emphasizes the great sensitivity of Hyper-CEST.

The selective detection of the presence of a membrane-associated cage pool becomes important when investigating the performance of novel Xe biosensors. Such biosensors comprise a Xe host (often CrA) that is linked to a targeting unit to form a functionalized NMR contrast agent. If the cryptophane-decoration on the surface of a targeted sensor is too exposed, unwanted interaction with the membrane can occur, as reported by Boutin *et al.* for a transferrin (Tf) receptor-based approach.¹¹ The characteristic second peak *ca.* 10 ppm downfield from the known peak of free Xe@Tf-cage could be observed in direct spectra. Such cage-induced binding effects to the membrane reduce the desired specificity of sensor uptake. Hyper-CEST detection is capable of detecting such a membrane-associated sensor pool at much lower concentrations and allows for reducing the cell density in solution. This aspect is of importance with regard to the relaxation of the hyperpolarized gas which can cause unwanted signal loss when surpassing certain cell concentrations. Additionally, the possibility to detect a reduced number of cells facilitates screening of xenon biosensors and allows an improved throughput.

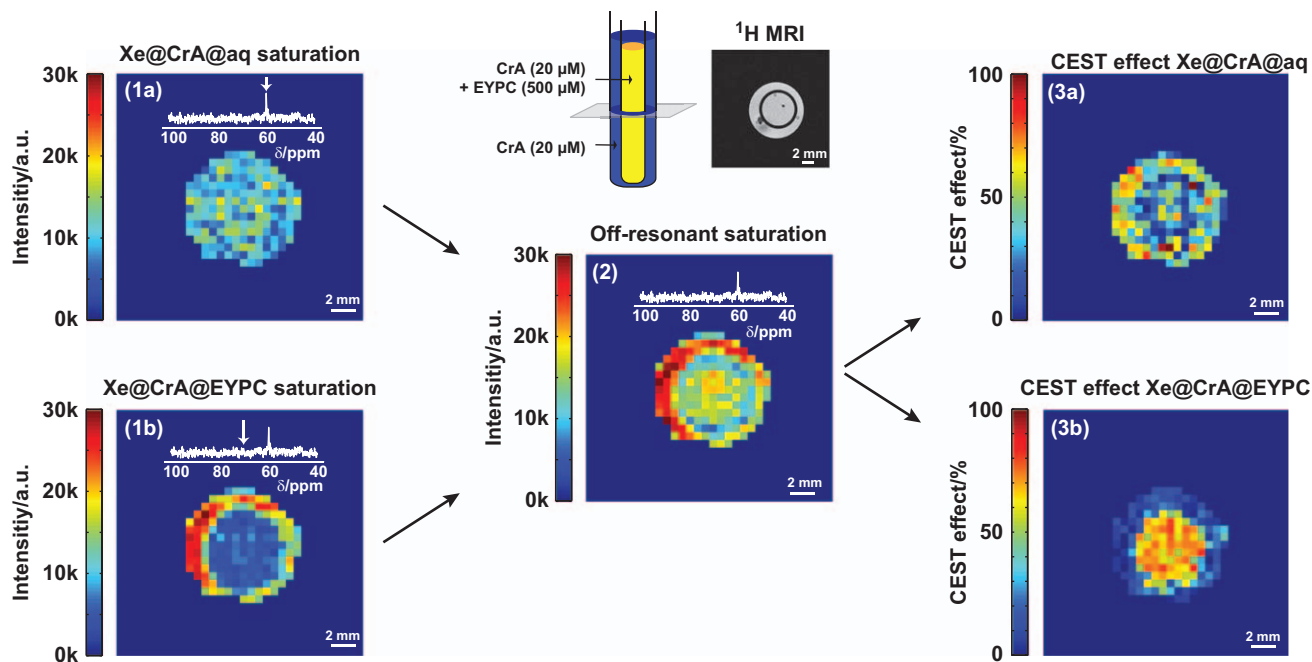


Figure 16.1 Hyper-CEST imaging of 500 μM EYPC with 20 μM CrA at 296 K. Applying a saturation pulse ($B_1 = 8 \mu\text{T}$, $t_{\text{sat}} = 8 \text{ s}$) at 60 ppm (1a) and dividing by the intensity after off-resonant saturation at 303 ppm (2) both compartments (a 5 mm NMR tube inside a 10 mm NMR tube) show up containing CrA (3a). Applying a saturation pulse at 71.5 ppm (1b) and dividing by the intensity after off-resonant saturation (2) only the inner compartment containing EYPC shows up (3b).

16.2 Investigating Membrane Dynamics Using Xe Hyper-CEST and DeLTA

As mentioned in Section 16.1 it is possible to detect the interaction of Xe and CrA with lipid bilayers. Along this line, Hyper-CEST MRI takes advantage of the chemical shift separation to selectively highlight areas that contain membrane material. This observation triggered experiments using various phospholipid compositions to further investigate whether discrimination of different membrane compositions would be feasible. Unfortunately, the chemical exchange for the Xe@CrA complex in lipid environment is relative fast and causes broad signals, both in direct detection as well as in CEST read-out. This is illustrated in Figure 16.2, where it can be seen that the position of the CEST dips can be determined very accurately but the width of the different CEST responses would not allow for separating different contributions in a mixture of phospholipids. Even for different membrane samples located next to each other discrimination in Hyper-CEST MRI by simple on- and off-resonance saturation would not be possible. It would

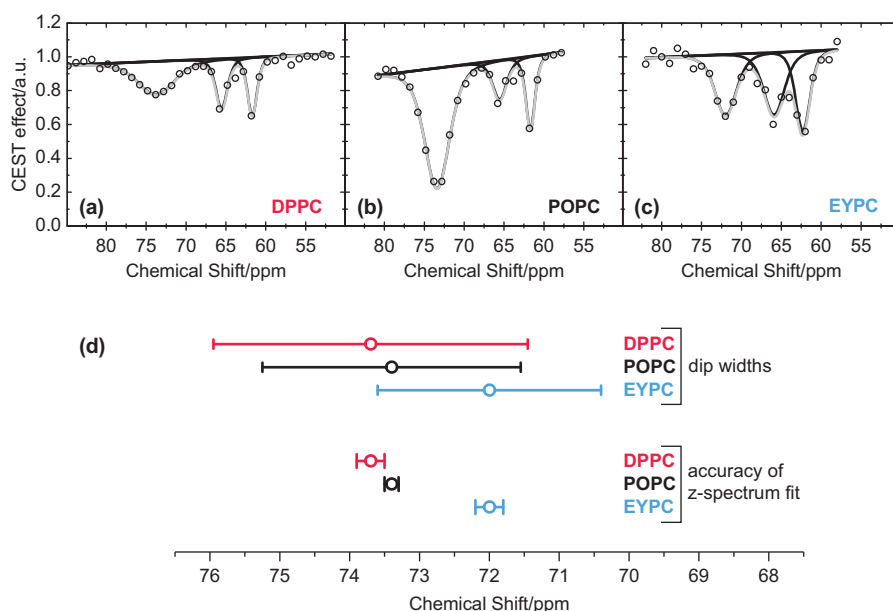


Figure 16.2 CEST-spectra of 200 μM DPPC (a), POPC (b) and EYPC (c) sensed with the fluorescence labelled cage CrA-DY682 (4 μM) at 25 $^{\circ}\text{C}$. Saturation parameters: $B_1 = 1.6 \mu\text{T}$; $t_{\text{sat}} = 8 \text{ s}$. The positions and the widths of the CEST-responses corresponding to Xe@CrA-DY682@lipid (always the far left signal) are plotted in (d). The far right and the middle signal are ascribed to monomeric Xe@CrA-DY682@aq and an aggregated form in aqueous solution, respectively.

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rather require (time-consuming) acquisition of a full z-spectrum. However, the intensity of the CEST effect in different membranes under otherwise identical conditions can be quite different. This is due to the sensitivity of the saturation transfer to the exchange dynamics,¹⁵ an effect initially demonstrated in pure aqueous environments with temperature changes.^{20–22} Hyper-CEST therefore allows information about the lipid bilayer's dynamics to be obtained in terms of fluidity probed *via* the Xe exchange behaviour, which is discussed in this section.

16.2.1 Discrimination of Solid-ordered and Liquid-disordered Membrane Phases

The xenon-host system can encounter different membrane conditions characterized by the fluidity of biomembranes. These are basically classified into three different phases: (i) a liquid-disordered (L_d) phase in which the phospholipids possess a high lateral mobility and are loosely packed, (ii) a liquid-ordered (L_o) phase which is also characterized by a high lateral mobility but a high degree of ordering of the phospholipids and (iii) a solid-ordered (S_o) phase in which also the lateral mobility is lowered.²

Membrane models consisting of pure saturated phospholipids such as DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine) are in the S_o phase at 295 K, whereas at this temperature membrane models of pure unsaturated phospholipids such as POPC (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) are in the L_d phase.²³ The different phases of these two model systems influence permeability for Xe and its intra-membrane mobility. This yields eventually different Hyper-CEST responses of Xe@CrA@lipid.¹² Although the responses are similar in chemical shift, they differ significantly in signal depletion. For example, the CEST effect of Xe@CrA@DPPC is *ca.* 20% in contrast to more than 80% CEST effect in POPC under otherwise identical conditions such as concentrations, temperature and saturation pulse parameters.^{12,24} Due to the similar chemical shifts for caged Xe in the different lipid bilayers, a possible contrast generation based on Hyper-CEST frequency separation for the different phospholipids is lost. However, taking advantage of variable saturation times allows for distinguishing DPPC from POPC membranes due to their different membrane fluidity. A tightly packed phospholipid bilayer like DPPC hampers the permeation of Xe atoms in and out of the bilayer. Additionally, such a highly ordered membrane reduces the Xe mobility inside the bilayer. These two effects together reduce the Xe depolarization rate and result in a reduced Hyper-CEST effect.

Although the different CEST effects can be explained very intuitively, an individual spectrum is not suitable for meaningful characterization of the membrane models. A useful measure is introduced by analysing the Xe Depolarization process using a Laplace Transform Analysis (DeLTA). This depolarization process is obtained by recoding the NMR signal of free Xe after applying saturation pulses of increasing length on the Xe@CrA@lipid

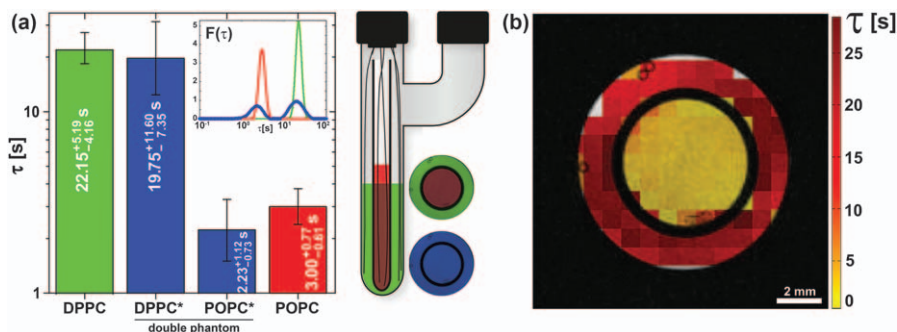


Figure 16.3 (a) Depolarization times τ obtained using DeLTA of DPPC in the outer compartment (green), POPC in the inner compartment (red) and of the bi-exponential depolarization process when analysing the whole double phantom (DPPC* and POPC*, blue). The corresponding depolarization time distribution $F(\tau)$ is shown in the inset. (b) Depolarization-time map of the double phantom obtained *via* a pixel-wise DeLTA superimposed with a ^1H MR image.

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resonance. The Laplace transform relates the observed (multi-) exponential decay (here the controlled depolarization processes) to a continuous distribution of dampers, here the depolarization times τ . Thus the number of depolarization times and their value can be obtained without requiring any prior knowledge. They make it possible to detect and characterize phospholipid environments which differ in membrane fluidity.¹² If two such different lipid environments are spatially separated, the overall depolarization process in the total volume is bi-exponential. However, the depolarization process in a single, enclosed compartment is mono-exponential. An example is shown in Figure 16.3. The inner compartment of the double phantom contains pure POPC liposomes and the outer compartment pure DPPC liposomes. Analysing individually the depolarization processes of the pixels in a Hyper-CEST MRI can therefore yield a detailed depolarization map of the Xe atoms. This map is directly related to differences in the fluidity of the phospholipid bilayers.

16.2.2 Cholesterol Level Determination

Besides saturated and unsaturated glycerophospholipids such as DPPC or POPC and sphingolipids, which contain a sphingosine backbone and typically a long, saturated acyl chain, cholesterol is the third main component of mammalian cell membranes, which can make up to 50 mol% of the membrane.^{25,26} Changes of the cholesterol content in cell membranes can result in dramatic effects on several types of membrane traffic. Incorporation of the almost entirely non-polar cholesterol molecules into POPC bilayers can induce formation of a liquid-ordered (L_o) phase,²⁷

which is characterized by a reduced passive permeability²⁸ and an increased ordering of the acyl chains.²⁹ Cholesterol even causes an L_o phase above the POPC's phase transition temperature.^{30,31} Basically, a cholesterol concentration of less than 15 mol% results in a L_d phase at 310 K. When the cholesterol concentration is increased up to *ca.* 45 mol% the L_d and L_o phases can coexist. In the coexistence regime lipid rafts can be formed.^{32,33} Lipid rafts are clusters of for example one type of phospholipids or sterols such as cholesterol that can move in the two dimensional plane of the membrane. At even higher cholesterol concentrations only the L_o phase is present.

The alteration in membrane traffic generated by a change of the cholesterol content also affects the Hyper-CEST response.²⁴ With higher cholesterol content the Hyper-CEST response of Xe@CrA@lipid becomes weaker. This agrees with the reduction of the Xe@CrA@lipid response when decreasing the fluidity and increasing the ordering of the phospholipids by replacing POPC with DPPC in pure liposomes (Section 16.2.1). Analysing the Xe@CrA@lipid response using DeLTA, the depolarization times τ range from 2.4 s for pure POPC to 8.9 s for a POPC : cholesterol molar ratio of 1 : 1 (thus still within the physiological range of cellular membranes). DeLTA measurements revealed that the depolarization time depends linearly on the cholesterol content of the membrane models and can be determined with an accuracy of at least 5% with respect to a reference with known cholesterol content.²⁴ In that context, DeLTA provides a complementary technique to established fluorescence techniques that can be used to measure the cholesterol content of membrane models.³⁴ However, being based on NMR, it is not limited by penetration depth.

16.2.3 Investigating Phase Transition Properties

Heterogeneous membrane models containing different types of phospholipids can differ significantly in their fluidity properties depending on their fractional composition. Lipid raft formation, for example, is one phenomenon that is determined by the lipid composition. This formation is subject to high fluctuations under certain conditions. An example are membrane models of POPC : DPPC mixtures. Since the net effect has an impact on the saturation transfer, it can be observed with DeLTA.

Decreasing the DPPC content in a POPC : DPPC membrane model from 100 to 98% increases the depolarization time τ drastically from 14.2 to 69.1 s.²⁴ Relatively long depolarization times ($\tau > 25$ s) are found for a POPC : DPPC ratio smaller than 1 : 4. For similar conditions the occurrence of lipid rafts was found to fluctuate highly dynamically as shown with simulations, calorimetric measurements, and fluorescence experiments.³⁵ Thus, this fast formation and vanishing of lipid rafts is considered to hinder an efficient Xe exchange in and out of the membrane, as well as the mobility of Xe and CrA inside the lipid bilayer yielding long depolarization times. With a POPC concentration larger than 25%, stable liquid domains are

formed which results in an efficient depolarization process. The process becomes more efficient with increasing content of phospholipids with unsaturated acyl chains (POPC). However, in membrane models that are mixtures of saturated and unsaturated phospholipids the depolarization processes are mono-exponential. The intra-lipid bilayer mobility of Xe and CrA in between the different membrane phases is presumably too fast for the time scale of Hyper-CEST containing a saturation pulse in the order of seconds. This is different in solutions containing homogeneous vesicles of pure DPPC and pure POPC. In this case, DeLTA yields bi-exponential depolarization processes at intermediate POPC : DPPC ratios. However, the two depolarization times are not as clearly separated as it is the case with POPC and DPPC vesicles being spatially separated (see Section 16.2.1).

16.3 From Membrane Models to Cells

Insights gained from different membrane models are helpful to interpret data from live cell investigations. So far, only a few fluorescence and NMR experiments with targeted and/or untargeted Xe hosts as biosensors have been performed with live cells,^{11,36–44} and only some of them took advantage of the sensitivity of Hyper-CEST.^{38–44} Throughout all NMR studies the Xe NMR resonance assigned to Xe@CrA@cells was found to be around 70 ppm, thus being very similar to the Xe@CrA@lipid resonance known from experiments with membrane models. This affirms that such models can be used in Xe biosensor studies for simplified and easy controllable experiments.

Beside the similar chemical shift, the partition effects of CrA and CrA labeled with a water-soluble fluorescent dye are consistent in cells^{39,40} and membrane models.¹³ The cage-dye conjugate bearing a hydrophilic unit shows reduced uptake into cells as is revealed by a weaker CEST response under otherwise identical incubation conditions (Figure 16.4). Efficient uptake triggered through pronounced hydrophobicity is, however, related to increased cell toxicity.^{39,40} The choice of different dye units for the cage seems to somewhat influence the chemical shift of the Xe signals, both for the free conjugate in solution as well as for the cell-associated molecules. This illustrates that there might be some room for optimizing the separation of the two peaks for better saturation transfer conditions in terms of reduced spillover effects between the two pools. Fluorescence labels allow for easy quantification of the cellular uptake and efficient planning of live cell NMR experiments.⁴⁰ Klippel *et al.* demonstrated unspecific uptake of CrA-dye conjugates in the micromolar range that is sufficient for fast MRI detection of labelled cells.³⁹

Whereas liposomes represent reasonably stable systems that can handle direct Xe bubble delivery into test solutions, live cells are more delicate. The shear forces of bursting gas bubbles compromise cell viability and extensive bubbling causes eventually a lot of cell debris that still carries embedded cages and Xe but with an unchanged NMR signature in the CEST

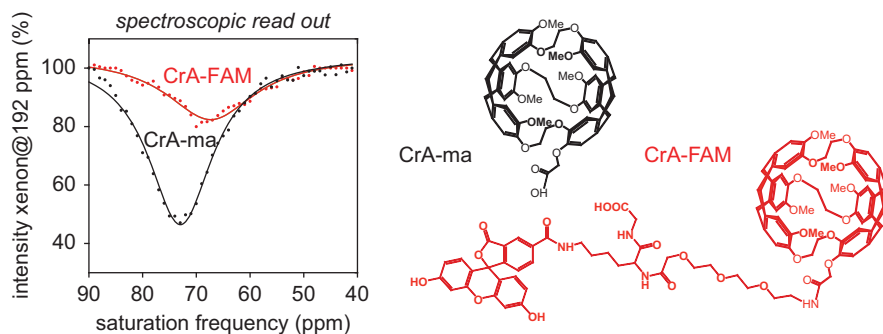


Figure 16.4 Comparison of the Hyper-CEST responses of labelled mouse fibroblasts (L929) in the perfusion phantom setup after incubation for 20 h with 50 μM of fluorescence-labelled CrA (CrA-FAM) and CrA-monoacid (CrA-ma). The stronger Hyper-CEST response of CrA-ma is presumably due to higher uptake of CrA-ma compared to the uptake of less hydrophilic CrA-FAM. Reproduced with kind permission from Klippel *et al.*³⁹ Copyright © 2013 Wiley-VCH.

spectrum.^{39,40} This has to be considered when designing experiments where the viability of the cells is desired throughout the experiment. Pines and coworkers reported that different cell lines react quite differently to this kind of mechanical stress.³⁸ The problem can be solved by using a perfusion phantom setup in which the Xe gas delivery into the solution is spatially separated from the NMR detection volume. The latter one carries immobilized cells (*e.g.* in terms of alginate beads that prevent wash out) and is perfused with cell culture medium that has been saturated with the hyperpolarized nuclei.^{39,42,45} Such a setup allows detailed studies of Xe in cellular environment with excellent viability conditions. Using such a perfusion setup, the time window for Xe live cell NMR experiments is increased significantly. These more physiological conditions will allow further insights into membrane biophysics that benefit from the high sensitivity and non-invasiveness of Hyper-CEST NMR.

16.4 Conclusions

Phospholipid membranes provide ideal conditions for Xe NMR experiments since they come with high solubility of the noble gas and can be paired with saturation transfer techniques (Hyper-CEST) to increase both sensitivity and specificity of the detected signal. Suitable molecular hosts like cryptophane cages partition into the membrane and enable investigation of dynamic parameters like membrane fluidity. The observable effects are helpful to characterize the behaviour of Xe biosensors as MRI contrast agents. Moreover, certain *in vitro* applications have the potential to further elucidate the behaviour of different heterogeneous membrane models for biophysical studies on membrane fluidity and integrity.

Acknowledgements

This work has been supported by the European Research Council under the European Community's Seventh Framework Programme (FP7/2007–2013)/ERC grant agreement no. 242710, the Leibniz Association (WGL; grant SAW-2011-FMP-2), and the Human Frontier Science Program.

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Continuous Flow and Dissolved Phase ^{129}Xe NMR/MRI for Quantification in Preclinical Study as well as Materials Science

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17.1 Introduction

HP ^{129}Xe has become an emergent approach in the morphological and functional analysis of organs such as the lung and brain in MRI and MRS for preclinical as well as clinical evaluation.^{1–6} When inhaled it exhibits extremely enhanced NMR signals at around 200 ppm, which originate from a dissolved-phase of lung tissue and blood, in addition to a gas-phase signal at

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

0 ppm. These characteristics make it possible to determine unique functional parameters of lungs by use of not only the gas-phase signal but also the dissolved-phase signal. These parameters are related to ventilation, gas-exchange and perfusion. Furthermore, HP ^{129}Xe is transferred from the lungs to the brain through blood flow and the dissolved-phase signal can be obtained from blood and tissues in the brain. Here, the longitudinal relaxation time of ^{129}Xe in brain tissue (T_{1i})^{7,8} can be determined in relation to brain functional parameters such as the level of oxygenation.

In preclinical studies with small animals such as mice, observation of the dissolved-phase signal turns out to be difficult because of the small volume of the phase (2–3%) and low solubility of ^{129}Xe with short relaxation time. The situation becomes further complicated because of the signal loss from the depolarization effect induced by radiofrequency (RF) pulses and by the non-renewable nature of hyperpolarized magnetization. Studies with mice, however, may be worthwhile since mice are commonly used in preclinical studies for different purposes where wide ranges of disease models are exploited, including genetically altered ones. For successful observation of the dissolved-phase signal from mice, it is necessary to enhance the polarization level as much as possible together with optimization of the measurement conditions. For this purpose, more than a decade ago we developed a continuous flow mode apparatus to produce HP ^{129}Xe and proposed a simple system to measure the MRI/MRS.^{9–13} The short polarization time of ^{129}Xe allows a constant delivery of stable and fresh HP ^{129}Xe or ^3He gas to the subject. In this chapter, the requirements for the system and a few examples of its applications are described.

17.2 Continuous Flow Mode Production of HP ^{129}Xe

The production of HP ^{129}Xe gas is usually performed under a batch mode where HP ^{129}Xe gas is separated by solidification in liquid nitrogen just after hyperpolarization. A small amount of N_2 , the quench gas, and a large volume of He, the buffer gas, are included as foreign gases, as they are useful for the achievement of higher polarization. In this method the solidified Xe is sublimed into a reservoir bag just before use. In contrast, in our original apparatus, ^{129}Xe is polarized in a continuous flow mode where the source gas including the quench gas is hyperpolarized online and supplied to the subject directly after mixing with O_2 gas. The polarization was performed by the well-known spin-exchange optical pumping (SEOP) method near atmospheric pressure at first¹⁴ and then under a reduced pressure.^{11,15} Enhancement of the polarization under reduced pressure was reported from a batch mode experiment,¹⁶ and we succeeded in introducing the results into our continuous flow mode. With the reduced pressure mode, the polarization level is increased to more than twice that achievable with near-atmospheric pressure mode. This is due to the decreased Xe partial pressure, which leads to the higher polarization in Rb and to the increased lifetime of the van der Waals complex including Rb and Xe. The pressure of 0.15 atm was chosen so as to maximize the signal to noise ratio (SNR) of the output

gas, and the ^{129}Xe polarization of 10–20% was attainable with an easy-to-construct and handle purpose-built apparatus. The HP ^{129}Xe can be continuously supplied to the subject at a flow rate as high as 4 L h^{-1} . Here, the N_2 was mixed at 30% as a quenching agent, as this ratio had been determined to maximize the SNR. Recently, we found that the use of a high-boiling point gas instead of N_2 increases the SNR 2–3 times. The high-boiling point gas can be removed from the system by condensation after polarization. For example, the use of isobutene instead of N_2 as a quench gas proved to be useful in enhancing the SNR by our experiments in which the isobutene gas could be removed from the hyperpolarized gas mixture by cooling and condensing it at -90°C out of the polarizing cell. The SNR obtained was 3 times higher than that obtained by using N_2 . In the experiments, the ^{129}Xe signal was monitored every 15 seconds for more than 10 min before and after switching the quench gas from N_2 to isobutene while maintaining the flow rate of Xe at 24 mL min^{-1} and those of N_2 and isobutene at 24 mL min^{-1} and 50 mL min^{-1} , respectively. Thus, the pure HP ^{129}Xe gas can be supplied continuously online from the system without including any foreign gases.

17.3 HP ^{129}Xe Delivery to Mice by Spontaneous Breathing

The application of HP gases to animal lung MRI has usually been performed under a volume- or pressure-controlled mode using a respirator device,^{17–19} where HP ^{129}Xe gas is supplied from a reservoir bag into which HP ^{129}Xe has been filled by subliming the solidified HP gas. Although the respirator-controlled mode has numerous advantages in obtaining stable respiratory synchronized signals, the resulting information does not reflect the lung structure and functions under normal breathing conditions. Therefore, we employed the spontaneous breathing mode under continuous delivery of HP gases, which is entirely noninvasive without any tracheal intubation or invasive tracheotomy and avoids the potential for side effects such as ventilator-associated lung injury.^{9–13,20} Moreover, it avoids cumbersome consideration of the depolarization effect occurring in a reservoir bag, which can be caused by the relaxation time in the gas reservoir ($T_{1,\text{R}}$),^{21,22} – this may change with conditions such as the size and shape of the reservoir as well as with time.²³ The T_1 of HP ^{129}Xe is strongly dependent on the environment and the paramagnetic oxygen leads to an increase in relaxation. Furthermore, the spontaneous breathing mode under continuous delivery of HP gases allows us to perform long-term and repeated measurements on the same individual, which is often important for preclinical evaluation.

17.4 Some Features of the Dissolved-Phase HP ^{129}Xe MRI/MRS *In vivo*

The dissolved-phase HP ^{129}Xe signals from rats and dogs appear mainly at around 190 ppm, 197 ppm and 212 ppm, which are assigned to the Xe inside

fat, tissue and blood, respectively.^{1,24} CSI images were reported for rats using these dissolved-phase signals as well as the gas-phase ones.¹

The spectral profile slightly differs for mice since the signal from blood appears at around 200 ppm.²⁵ To the best of our knowledge, dissolved-phase images of mice have only been reported by the author's group^{13,26} until quite recently.²⁷

17.5 Protocols for Dissolved-Phase HP ^{129}Xe MRI/MRS Experiments *In vivo*

The protocols of our experiments are described below for the dissolved-phase HP ^{129}Xe MRI/MRS of mice using the wide-bore 9.4 T magnet.

17.5.1 Animals

All experimental procedures and animal care strictly conformed to our university's guidelines. Typically, male ddY mice aged 6–8 weeks were used. In the HP ^{129}Xe MR experiments, a plastic mask was attached to the mouth of the mouse, to which fresh HP ^{129}Xe gas was continuously supplied after being mixed with O_2 just before entering into the mask. The mouse would thereby spontaneously inhale the mixed gas flowing through the mask. The final composition of the mixed gas was 20, 24 and 56% for O_2 , N_2 and Xe, respectively. MR measurements were started when a steady state was reached for the ^{129}Xe MRS signal from the lung.

After the MR experiments, mice were killed with a lethal dose of carbon dioxide. The lungs were processed for conventional histology and stained with hematoxylin and eosin (H&E). Mean linear intercepts (L_m), alveolar septal thickness ($h_{\text{histology}}$) and the septum-to-alveolar volume ratio ($V_s/V_{\text{a histology}}$) were calculated.²⁸

17.5.2 ^{129}Xe Hyperpolarizer

The apparatus comprised gas-storage, a purifier, flow controllers and a SEOP glass cell located in an oven maintained at 110 °C. The source of HP ^{129}Xe , a mixture of 70% Xe (natural abundance of 26.4% ^{129}Xe) and 30% N_2 , was continuously supplied at a flow rate of 24 mL min⁻¹ to the SEOP cell operating at 0.15 atm. The SEOP cell (Pyrex polarizing cell, 1.4 L), in which a droplet of rubidium was deposited, was placed in the fringe field (about 12 mT) of a NMR magnet. Circularly polarized light was irradiated at 795 nm into the cell to perform the optical pumping using laser diode arrays. Polarization of 10–20% was obtained under 90 W laser power with FWHM = 2 nm. This polarization can be increased by adopting the advanced narrow band laser: a recent experiment demonstrated that a 30 W narrow band laser with FWHM = 0.35 nm can increase the polarization threefold compared with the old type having FWHM = 2 nm at the same output power.

A diaphragm pump was used to maintain the reduced pressure in the SEOP cell and to flow the HP gas at an atmospheric pressure.

17.6 Dissolved-phase HP ^{129}Xe MRS

17.6.1 Origin of the ^{129}Xe Signals from Mouse Lungs

Figure 17.1(a) shows the dissolved-phase HP ^{129}Xe MRS obtained from a mouse lung under spontaneous breathing conditions.²⁵ Typical acquisition parameters of the MRS were: spectral bandwidth of 50 kHz, data complex points of 48 k, flip angle of 30° , and TR of 3.4 s. As shown in Figure 17.1(a), three dissolved-phase signals were consistently observed at 192 ppm (A), 196 ppm (B) and 200 ppm (C) for mice. The continuous delivery of stable fresh HP gas can enhance the spectral quality through signal averaging after repeated measurements. Thus, the MRS magnetization transfer experiments successfully confirmed the origin of the dissolved-phase signals *ex vivo* as well as *in vivo*: we could obtain experimental evidence to assign the three dissolved phase signals at 192 ppm, 196 ppm and 200 ppm to epicardial fat (A), lung parenchyma tissue (B) and blood (C), respectively. It should be noted that the signal dissolved in red blood cell (RBC) is not observed at around 210 ppm for mice, differently from other species including rats.²⁵ This difference is due to a difference in the exchange rate of ^{129}Xe between the components of blood, plasma and hemoglobin, that is probably faster in mice than in other species.

17.6.2 2D MRS of the Dissolved-phase ^{129}Xe Signals

The continuous delivery of stable fresh HP gas also made it possible to visualize and validate the exchange phenomenon of HP ^{129}Xe between the gas- and dissolved-phase signals in the 2D exchange MRS (2D-EXSY) as shown in Figure 17.1(b).²⁹ Figure 17.1(b) was obtained by the 2D-EXSY pulse sequence, $\text{PD}-90^\circ-t_1-90^\circ-t_m-90^\circ-t_2$, where PD is the pre-delay time, t_1 and t_2 are the evolution and the FID detection period, respectively, and t_m is the mixing time during which spin transfer occurs by the exchange process and causes cross peaks to appear between diagonal peaks in the 2D spectral map. The measurement conditions were typically: spectral band width of 32 kHz; PD of 4 s; accumulation time of 8–16 scans. The mixing time was set to 12 ms. Data sets with F_1 and F_2 dimensions of 32 and 512 were collected and then zero-filled to 128 and 512, respectively.

In the study, we succeeded in the 2D-EXSY MRS experiment and in the observation of the gas exchange phenomena *in vivo*. In the spectrum (Figure 17.1(b)), the cross peaks clearly indicated the existence of exchange of HP ^{129}Xe magnetizations between the two phases. This phenomenon is extensively exploited in HP ^{129}Xe MRI/MRS to quantitate the lung structure and function of gas-exchange.^{28,30,31}

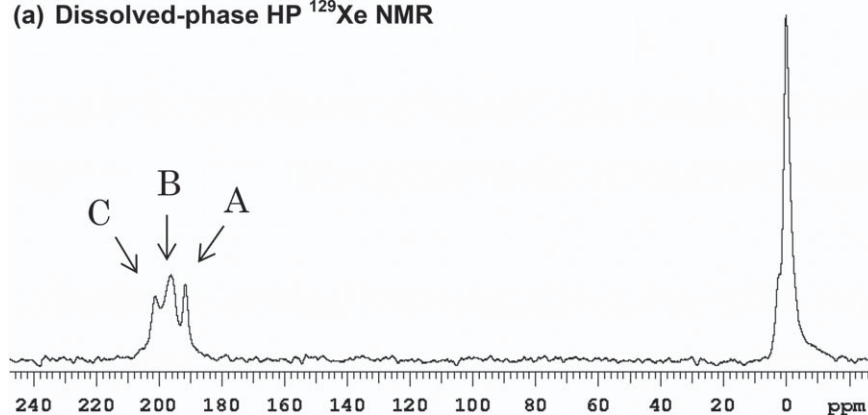
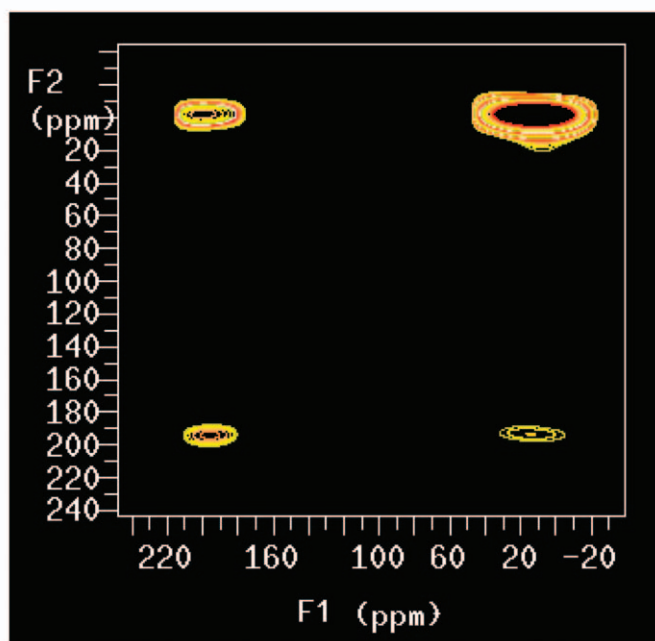
(a) Dissolved-phase HP ^{129}Xe NMR(b) 2D EXSY *in vivo*

Figure 17.1 Dissolved-phase HP ^{129}Xe MR spectra obtained from chest of mouse. (a) 1D NMR spectrum (reprinted from ref. 25). Assignment of the dissolved phase signals is: epicardial fat (A), lung parenchyma tissue (B) and blood (C). (b) 2D-EXSY spectra. Appearance of the cross peaks supports a successful detection of ^{129}Xe exchange between gas (0 ppm) and dissolved (192–200 ppm) phases.

This exchange phenomenon is also examined with a mouse model of cancer in 1D MRS wash-out experiments.³² A product of the rate constant for Xe transfer from gas to dissolved phase (k_1) and from dissolved to gas phase

(k_2), which has been successfully determined from the analysis of HP ^{129}Xe dynamic experiments under spontaneous respiration, is shown to increase by 60% in mice injected with B16BL6 melanoma cells compared to those in healthy mice.

17.7 Lung Structure Evaluated by HP ^{129}Xe MRS

The lung structure can be evaluated by analysis of the chemical shift saturation recovery (CSSR) of the dissolved-phase signal in which two parameters of alveolar septal thickness, h_{CSSR} , and septum-to-alveolar volume ratio, $V_s/V_{a,\text{CSSR}}$, are obtained in addition to the mean transit time of blood through the gas exchange region, MTT , as a pulmonary functional parameter.^{28,30} In this method, the recovery process during the delay time after selective saturation is measured (Figure 17.2(a)). This dynamic profile reflects the amount of ^{129}Xe diffused from the gas-phase to the septum during the delay time and can be analyzed using a simple model of ^{129}Xe septal uptake (Figure 17.2(b)), leading to evaluation of the three parameters. These structural parameters derived from the CSSR methods are consistent with those from histological analysis, $h_{\text{histology}}$ and $V_s/V_{a,\text{histology}}$ (Table 17.1).

The CSSR results were compared between healthy and elastase-induced emphysematous mice lungs. Histological comparison of the two mice clearly showed a breakdown of the alveolar walls in the elastase-treated mouse. These tendencies were consistent for all mice that we measured.

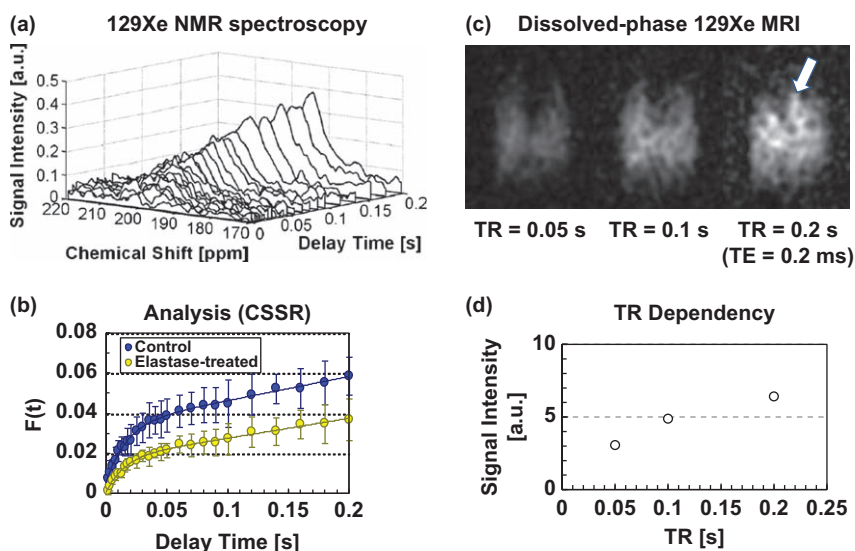


Figure 17.2 HP ^{129}Xe dynamic spectroscopy and its extension to imaging experiments as applied to the chest of mouse (reprinted from ref. 28 and 31). (a) CSSR spectra. (b) Analysis of the CSSR spectra. (c) TR dependent images obtained with the UTE sequence. (d) TR dependency of the total signal intensity in the dissolved-phase images.

Table 17.1 Parameters determined from the CSSR measurement and histology.^a

Type of Mouse	CSSR		Histology	
	<i>h</i>	<i>V_s/V_a</i>	<i>h</i>	<i>V_s/V_a</i>
Naïve	5.42 ± 0.84	0.364 ± 0.066	4.13 ± 0.44	0.252 ± 0.061
Control	6.89 ± 1.07	0.343 ± 0.050	5.51 ± 1.19	0.281 ± 0.044
Elastase treated	7.23 ± 1.54	0.206 ± 0.051	6.34 ± 1.77	0.135 ± 0.028

^aAverages for 3 (Naïve) and 6 (control and elastase treated) mice are listed with standard deviations.²⁸

In Figure 17.2(b), the initial buildup of the recovery curve of the elastase-treated mouse is slower than that of the healthy mouse, reflecting the increase of septal thickness (h_{CSSR}). Furthermore, the relative intensities of the dissolved-phase signal, $F(t)$, for the elastase-treated mouse are significantly lower than those of the healthy mouse throughout the delay time, reflecting the reduction in volume ratio ($V_s/V_{a\text{CSSR}}$).

17.8 Dissolved-phase HP ¹²⁹Xe MRI in Mouse Lungs

Because the spectroscopic analysis stated above offers only a whole-lung profile and not the spatial information, it is important to extend it to the imaging study using dissolved-phase signals which will be useful to identify a lesion. Although such imaging is difficult due to the weak intensity and short transverse relaxation time, T_2^* , it has become feasible by incorporating advanced techniques. In the case of mice, ultrashort echo-time (UTE) pulse sequence under the spontaneous breathing condition has given such dissolved-phase images as shown in Figure 17.2(c).¹⁹ The images were acquired by using a non-slice selective UTE sequence with a 90° flip angle, TE of 0.2 ms, NEX of 64, and a spatial resolution of 0.31×0.31 mm².

Figure 17.2(c) shows the dissolved-phase images obtained at three different delay times of the repetition time TR. The signal intensity in dissolved-phase images reflects the Xe uptake from the gas-phase to tissue and blood when TR is short, and then indicates the transfer by blood flow when TR is long. Thus, it can be an imaging version of the CSSR spectroscopy. In fact, the total signal intensity in the dissolved-phase images changes with TR in a similar manner to that in the CSSR spectroscopy (Figure 17.2(d)). The ¹²⁹Xe signal in the left upper region outside the lung (arrow) observed at the TR of 200 ms is different from that obtained at the TR of 50 ms and may originate from the pulmonary vein.

Figure 17.3 shows successful examples of dissolved-phase imaging performed with different TE from 0.2 to 1.0 ms. The dissolved-phase ¹²⁹Xe image was observable with short TE, as short as 0.2 ms, while it was difficult to observe with the longer TE such as longer than 1 ms mainly because of the rapid T_2^* decay. T_2^* can be calculated from the TE dependency and $T_2^* = 0.67 \pm 0.30$ ms was obtained as a mean value from a T_2^* map created from TE dependency of the dissolved-phase HP ¹²⁹Xe images.

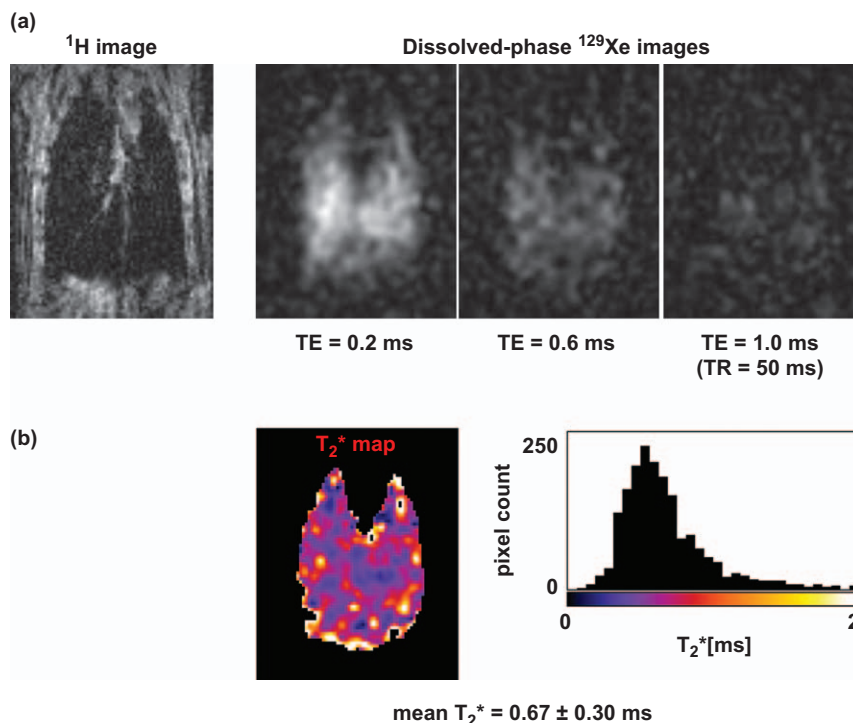


Figure 17.3 Dissolved-phase ^{129}Xe lung images obtained with variable TEs (reprinted from ref. 31). (a) ^1H image and ^{129}Xe images acquired with TE of 0.2, 0.6, and 1.0 ms (from left to right) under TR = 50 ms. (b) T_2^* map created from the ^{129}Xe dissolved-phase images measured under different TEs (left) and its histogram (right).

Figure 17.4 shows an example of the dissolved-phase images compared with the gas-phase ones measured with the control as well as with elastase-treated mice. The signal intensity in the dissolved-phase image is lower than that in the gas-phase one for the elastase-treated mouse, which reflects the reduced uptake efficiency due to the decrease in V_s/V_a by alveolar destruction. To quantitatively assess the uptake efficiency, the parameter F has been proposed, which is obtained from the signal intensity in the dissolved-phase image divided by that in the gas-phase one and is considered to visualize the ^{129}Xe dissolved-phase magnetization that has diffused into septa. Here, normalization is taken to the gas-phase magnetization. The mean F value thus calculated was reduced significantly in the elastase-treated mice and correlated with the histologically-derived alveolar surface-to-volume ratio ($V_s/V_{a \text{ histology}}$), supporting successful visualization of the uptake efficiency in the lung.

In mice, the dissolved-phase imaging and CSSR measurements were not applicable to observe the RBC signal separately. This is peculiar to mice among different species of animals and is probably induced by the fast ^{129}Xe

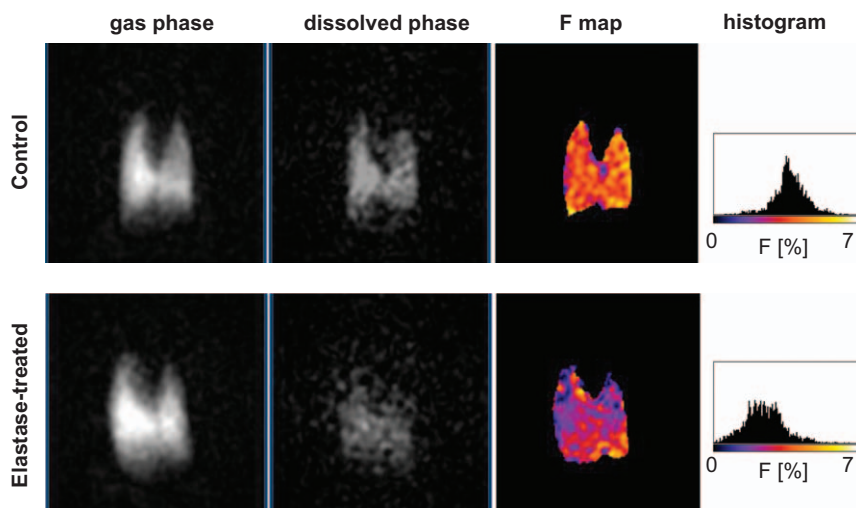


Figure 17.4 Quantification of the uptake efficiency in the lung by means of F value. Gas-phase and dissolved-phase ^{129}Xe images acquired from control (upper row, 1st and 2nd columns) and elastase-treated mice (lower row, 1st and 2nd columns) together with the F map (third column) and its histogram (fourth column). Reprinted from ref. 31. See text for details.

exchange in the blood components of RBC and plasma, resulting in a signal coalescence that participates in the exchange phenomenon. Recently, however, an HP ^{129}Xe study using transgenic mice expressing human hemoglobin has reported that the dissolved-phase image was obtained separately for RBC and barrier tissues (blood plasma and parenchyma), expanding the utility of mice in the dissolved-phase ^{129}Xe study.²⁷

17.9 HP ^{129}Xe MRS from Mouse Brain

The dissolved-phase signal can be obtained from the head of mouse after inhalation of the HP ^{129}Xe gas, and hence one can measure the uptake and washout dynamics in the mouse brain.^{8,33} An uptake model³⁴ derived from Kety's inert gas exchange model with Fick's principle, which has been discussed for human study, should be applicable. However, the very weak signals in the mouse brain have prevented reliable quantitative analysis of the uptake and washout dynamics. Furthermore, the analysis is seriously complicated by the depolarization effect induced by RF pulses: the time-dependent concentration of HP ^{129}Xe , C_i , contains the term related to a RF pulse as follows for the uptake process as derived from Fick's principle,

$$\frac{dC_i(t)}{dt} = F_i C_a - \left(\frac{F_i}{\lambda_i} + \frac{f(1 - \cos \theta)}{\text{TR}} + \frac{1}{T_{1i}} \right) C_i \quad (17.1)$$

where F_i is the global cerebral blood flow (CBF) measured in mL of blood per mL of tissue per second, C_a is the concentration of HP ^{129}Xe in the arterial blood that reaches the brain tissue, λ_i is the partition coefficient between the tissue and the blood, and T_{1i} is the longitudinal relaxation time in the brain tissue. In eqn (17.1), the depolarization by a RF pulse at a flip angle is taken into account as a constant rate term, $f(1 - \cos\theta)/\text{TR}$ where TR is the interval between two RF pulses, and f denotes the portion of HP ^{129}Xe magnetization which remains after TR from a depolarization. The portion, f , approaches 1 or 0 when the uptake rate of HP ^{129}Xe is much smaller or larger than the depolarization rate, respectively.

By contrast, the analysis is greatly simplified by applying the saturation recovery measurement to the dissolved-phase signal under a spontaneous breathing condition, and eqn (17.1) can be simplified to eqn (17.2) where ambiguities from the RF depolarization effect are removed,

$$\frac{dC_i(\tau)}{d\tau} = F_i C_a - \left(\frac{F_i}{\lambda_i} + \frac{1}{T_{1i}} \right) C_i \quad (17.2)$$

where τ is the recovery time from a saturation pulse. The basis of this simplification is obvious from the fact that the HP ^{129}Xe magnetization in the lung is in a steady state and starts to diffuse into the brain tissue immediately after the saturation. As a result, the time-dependent signal intensity during the saturation recovery process is easily analyzed according to eqn (17.3):

$$S(\tau) = \eta C_i(\tau) = \frac{\beta}{\alpha} (1 - e^{-\alpha\tau}) \quad (17.3)$$

with

$$\alpha = \frac{F_i}{\lambda_i} + \frac{1}{T_{1i}} \text{ and } \beta = \text{Const.}$$

where η is the parameter that normalizes the concentration of HP ^{129}Xe in the brain tissue to the NMR signal amplitude. A typical experimental result is depicted in Figure 17.5.

Thus, it was possible to estimate the T_{1i} of HP ^{129}Xe in the mouse brain as 15.3 ± 3.5 seconds.⁸ This methodology with a continuous-flow mode of stable fresh HP ^{129}Xe will be effectively applied to brain functional analysis.

17.10 Utility of the ^{129}Xe NMR Signals in Material Analysis

In analogy with the *in vivo* MRS, nuclear magnetic resonance (NMR) of ^{129}Xe is also known to serve as a sensitive tool for analyzing the structural and physicochemical properties of various materials by taking advantage of the dissolved-phase signals of HP ^{129}Xe that carry unique information about the chemical characteristics of specific molecular interactions in the

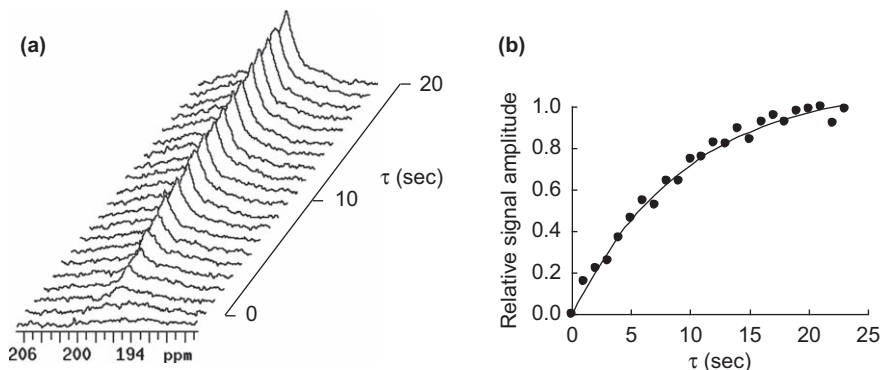


Figure 17.5 HP ^{129}Xe saturation recovery experiments with the brain of mouse under the continuous-flow condition (reprinted from ref. 8). (a) Time dependent ^{129}Xe dissolved-phase signals in MRS. (b) The τ value dependency analyzed to give $T_{1i} = 15.3 \pm 3.5$ s.

material. In this section our continuous flow mode hyperpolarizing system is also shown to be useful for these studies when used with a bubbling technique to supply stable fresh HP ^{129}Xe signals in solution.

17.10.1 2D-HOESY Experiments

2D-HOESY (Heteronuclear Overhauser Effect Spectroscopy) spectra are a powerful tool to detect intermolecular interactions in solution in organic chemistry. Here, 2D $^{129}\text{Xe}\{^1\text{H}\}$ HOESY was tested to determine whether it can provide any information on the interactions between Xe and organic molecules taking ethylbenzene (C_8H_{10}) and diethyl phthalate ($\text{C}_{12}\text{H}_{14}\text{O}_4$) as examples. The data were acquired at 28 °C with a 10 mm NMR tube by adopting the pulse sequence: PD (pre delay)– t_b (bubbling time)– d_1 (relaxation delay)– $90^\circ(^1\text{H})$ – t_1 – $90^\circ(^1\text{H})$ – t_m – $90^\circ(^{129}\text{Xe})$ – t_2 . During the mixing time t_m , the HP ^{129}Xe magnetization is modulated by ^1H magnetization through the cross-relaxation between ^{129}Xe and ^1H , *i.e.*, through the SPINOE (Spin-Polarization-Induced Nuclear Overhauser Effect),³⁵ and it permits cross peaks to appear due to the heteronuclear proximity effect. The HP gas was continuously bubbled into the sample through a polyethylene tube duration t_b , and then the pulse sequence HOESY was started after a waiting time d_1 which was inserted to suppress the turbulent flow in the NMR tube. This cycle of HP gas supply and 2D measurement was repeated automatically until the number of transients needed for the 2D acquisition was reached.

A polarization transfer by SPINOE between ^1H and ^{129}Xe was clearly confirmed in the HOESY experiments (Figure 17.6). That is, cross peaks appeared between the dissolved ^{129}Xe peaks, 182.5 ppm in ethylbenzene and 190.5 ppm in diethyl phthalate, and the solvent ^1H peaks, 1.2, 2.6, and 7.4 ppm for CH_3 –, CH_2 –, and C_6H_5 – in ethylbenzene, respectively, and 1.3, 4.4, and 7.5 ppm for CH_3 –, CH_2 –, and C_6H_5 – in diethyl phthalate,

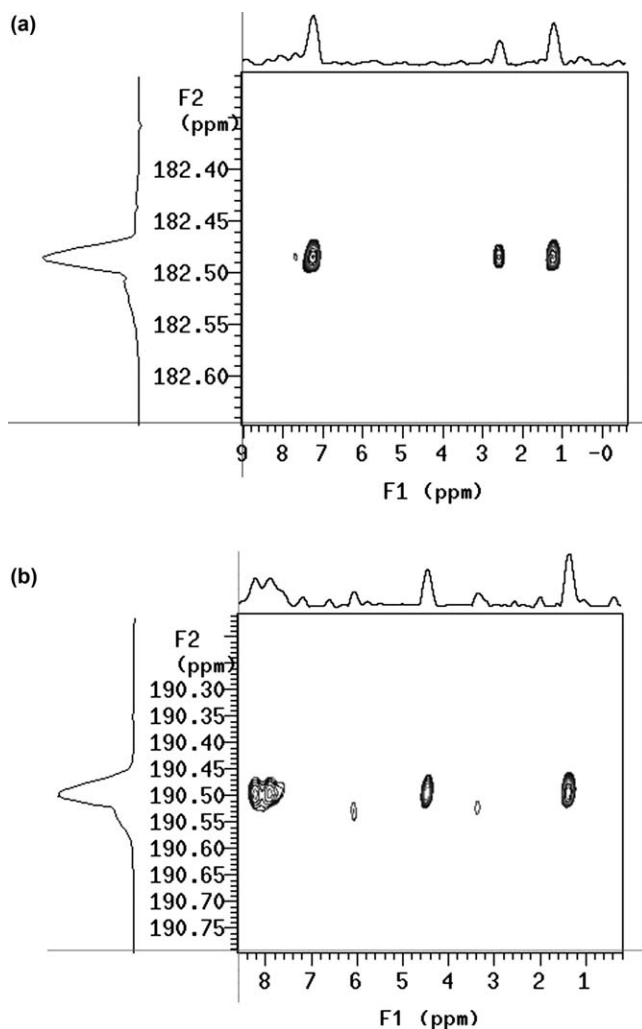


Figure 17.6 The 2 dimensional $^{129}\text{Xe}\{^1\text{H}\}$ HOESY spectra obtained in solution under bubbling of the HP ^{129}Xe gas. (a) Solvent: ethylbenzene. (b) Solvent: diethyl phthalate. Cross peaks are observed between the ^{129}Xe dissolved signal and the ^1H solvent signals. See text for further description.

respectively. This indicates the space proximity interactions between the nuclei connected by the cross peaks. Although our attempt to observe the 2D-HOESY spectra was successful and its extended application to biologically interesting molecules is encouraged in solution, the results did not show any significant evidence for site-specific interactions of Xe with protons, as reported³⁶ for the case of toluene, where preferential enhancement of the aromatic protons over the methyl protons has been observed in HP liquid Xe solution. The difference in experimental temperatures, 200 K *vs.* room temperature,³⁶ could explain this discrepancy.

17.10.2 2D-EXSY Experiments

In analogy with the case reported in 17.6.2, the 2D-EXSY experiment can be applied to porous materials where the HP ^{129}Xe adsorbed signal can be treated just like the dissolved phase signal in mouse lungs. In the case of Polygosil60, which is the chromatographic support from M. Nagel Co. Ltd., the exchange rate constants have been determined to be $11.5 \pm 1.8 \text{ s}^{-1}$ and $28.7 \pm 1.8 \text{ s}^{-1}$ for the exchange from gas to surface and from surface to gas, respectively, and values of $7.3 \pm 2.2 \text{ s}^{-1}$ and $64.7 \pm 19.4 \text{ s}^{-1}$, respectively, were obtained in the study with mouse alveoli.¹⁷ In the case of industrial materials, temperature dependent 2D-EXSY experiments have been applied successfully to provide with the activation energy for the exchange reaction: 37.2 kJ mol^{-1} and 38.5 kJ mol^{-1} were obtained for the Eyring enthalpy of activation for the exchange from gas to surface and from surface to gas, respectively, with the Polygosil60.

17.10.3 Supramolecular Complex Formation in Solution

The continuous flow hyperpolarizing system can be successfully applied to the study of intermolecular interactions in solution. Bubbling of the stable fresh HP ^{129}Xe gas into a solution brings the concentration and signal intensity of the dissolved phase ^{129}Xe to a stationary state, making the quantitative analysis of molecular interactions feasible. Inclusion complex formation of thiocalix[4]arene with Xe in water thus studied³⁷ has given the equilibrium constants for the reaction at different temperatures that led to thermodynamic parameters of enthalpy ΔH and entropy ΔS . The ΔH value of thiocalix[4]arene was about 1/2 to 1/3 those of the myoglobin derivatives studied in relation to the general anesthetic property of Xe. The entropy ΔS can be derived from the molecular theory of thermodynamic functions. This gives evidence for the release of a definite number of water molecules, *i.e.*, around 1.3–1.6 water molecules, on the formation of the supramolecular complex.³⁷

17.11 Conclusions

This article reviewed our recent progress in HP ^{129}Xe MRS/MRI. Utility of the continuous flow mode hyperpolarization was demonstrated and information derived from the dissolved-phase signals was summarized. We showed that MRS/MRI is useful to evaluate important physiological parameters in the mouse lung: perfusion, alveolar structure, and regional pulmonary gas exchange. Utilization of the dissolved-phase signals will provide new opportunities to comprehensively evaluate the pulmonary functions in terms of the three essential components of ventilation, gas-exchange, and perfusion, leading to successful evaluation and understanding of different lung diseases. The methodology will also be effectively applied to materials science where advanced fields of NMR such as 2D-NMR, HYPER-CEST, and

biosensors can play important roles, since it can provide stable fresh HP-Xe gas, either natural or isotopically-enriched, at as high as 70% Xe or even with no foreign gases in continuous-flow mode.

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Hyperpolarized Xenon-129 Gas Uptake in the Human Lung and XTC MRI

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18.1 Introduction

As a contrast agent for medical imaging, perhaps the most exciting characteristic of hyperpolarized xenon-129 (HXe) is its solubility in biological tissues. Unlike helium-3, inhaled xenon-129 does not remain confined to the lung airspaces but instead is readily absorbed into the various parenchyma tissues including capillary blood. Furthermore, there is a large downfield shift of the gas-phase resonance frequency (approximately 200 ppm) upon entering the dissolved phase,¹ and much smaller chemical shifts can often be observed within the dissolved phase resonance, arising from the different tissues present in the lung parenchyma.² These properties make it possible to generate image contrast based on xenon-129 uptake in the lung, thereby permitting functional characterization of the lung parenchyma itself, which is not possible using helium-3. Finally, since HXe is carried to other parts of

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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the body once it enters the bloodstream, potentially valuable information about the structure and function of other organs (most prominently the brain) can be obtained as well.^{3–6}

The simplest method for observing xenon-129 gas-exchange and distribution dynamics is global (single-voxel) MR spectroscopy. As demonstrated by Tseng *et al.*,⁷ Albert *et al.*,⁸ and Mugler *et al.*,² at least two dissolved-phase resonances can be identified for HXe in the lung: xenon-129 in the tissue and plasma (TP) at about 197 ppm (by convention, the free gas resonance is arbitrarily set to 0 ppm) and xenon-129 inside the red blood cells (RBCs) at about 210–220 ppm, with the latter shift somewhat dependent on the oxygenation level of the blood^{9,10} and the particular animal species being studied. The reason for this observed downfield frequency shift (*i.e.*, away from the plasma and gas peaks) of up to 5 ppm, which increases with increasing oxy-hemoglobin concentration, is believed to be conformational changes in the hemoglobin induced by oxygen binding.¹⁰ Based on the solubility coefficients, it can be inferred that 75% of the xenon dissolved in whole blood resides in the RBC with 45% of this subtotal weakly bound to hemoglobin.⁷ All compartments are in rapid exchange, with time constants on the order of 10 ms.¹¹

Although HXe dissolved in blood is subsequently transported throughout the body, the T_1 of xenon-129 is only a few seconds in the dissolved phase^{12–14} and the total fraction is relatively small, inhibiting the ability to accumulate measureable quantities in organs outside of the lung. Therefore, in living organisms, the lung itself is by far the easiest organ to assess with HXe magnetic resonance. The primary function of the lung is gas exchange, and the contrast properties of dissolved-phase xenon-129 allow this process to be investigated directly, using xenon-129 as a surrogate marker for oxygen. Once a HXe dose has been inhaled, the xenon quickly enters lung tissue and capillary blood through passive diffusion; no active transport processes are known. Xenon follows the same pathway as oxygen, passing from the alveolar air spaces into the liquid lining of the alveolus, then through the epithelium, the interstitium, the capillary endothelium and the blood plasma, before the xenon atoms eventually weakly bind to hemoglobin within the RBCs (see Figure 18.1a).

Although it is composed of several distinct tissue types, the air–blood barrier is less than 1 μm wide and the entire thickness of the alveolar septum (the thin wall that separates neighboring alveoli) is only about 5 μm .¹⁵ Depending on the particular animal species and the specific details of the acquisition method, the HXe uptake process gives rise to at least two, but possibly three or four, broad and overlapping peaks in the dissolved-phase region of the acquired NMR spectrum^{4,16,17} (Figure 18.1b). Two main factors contribute to the broad line width (and correspondingly short T_2^*) of the dissolved-phase xenon spectral peaks: (a) large magnetic field inhomogeneities caused by the 9 ppm magnetic susceptibility difference between parenchyma tissue and air¹⁶ and (b) the rapid exchange of the xenon atoms among the various frequency compartments, both of which lead to fast dephasing of the transverse magnetization.¹⁷

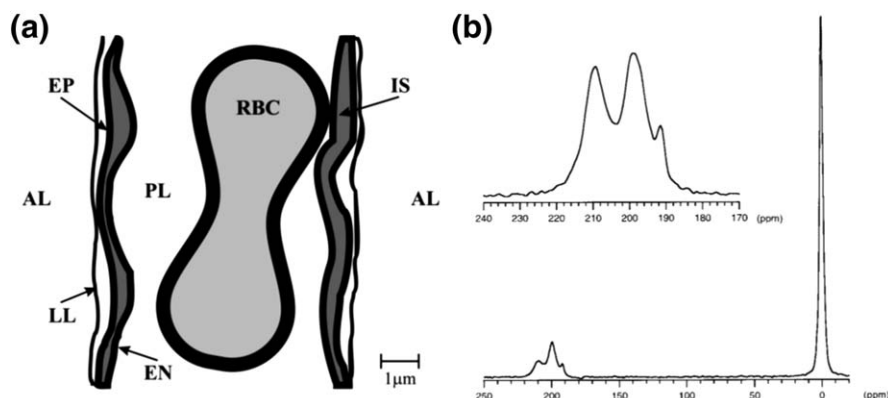


Figure 18.1 (a) Schematic of the alveolar wall structure based on electron micrographs. AL: alveolus; LL: alveolar liquid lining; EP: epithelium; IS: interstitial space; EN: endothelium; PL: blood plasma; RBC: red blood cell. The air–blood barrier is comprised of the alveolar liquid lining, epithelium, interstitial space, and endothelium. (b) *In vivo* NMR spectra of xenon-129 in the rat body. The full spectrum shows xenon-129 dissolved in blood, water-based tissue, and fat at 210, 199, and 192 ppm, respectively. Xenon gas in the lungs is arbitrarily set to 0 ppm. (a) Copyright 2000 Magnetic Resonance in Medicine. (b) Reprinted with permission from Swanson *et al.* (1999). Copyright 1999 Magnetic Resonance in Medicine.

18.2 Spectroscopic Measurements

Possibly the easiest way to study the dynamics of HXe gas exchange in the lung is to suddenly begin continuously ventilating the subject with an air–xenon mixture.^{18,19} Through the repeated acquisition of NMR spectra, a wash-in process is observable during which the dissolved-phase signal amplitudes increase until they asymptotically approach a maximum value through tissue saturation.^{16,20} If HXe is then suddenly removed from the gas mixture, the dissolved-phase xenon signal begins to drop as the xenon atoms are either washed out of the tissue or their polarization decays away. The three dissolved-phase peaks identified in healthy mice reach their maximum size in about 5 to 10 s and subsequently decay with time constants approaching 30 s.¹⁶ It is reasonable to expect that these time constants may change for certain lung diseases, such as lung cancer, that alter the overall pulmonary blood flow patterns and therefore should affect the resulting HXe distribution.²⁰ Wolber *et al.* suggested that some tumor types may even give rise to additional unique dissolved-phase spectral features.²¹

The non-equilibrium nature of the HXe magnetization also greatly facilitates the measurement of xenon atoms moving from one frequency compartment to another. HXe does not experience T_1 -driven signal recovery following RF excitation, since the thermal equilibrium polarization towards which the spin system is driven by T_1 relaxation is 4 to 5 orders of magnitude

lower than the hyperpolarized magnetization and is therefore essentially zero. If the magnetization of all HXe atoms dissolved in lung tissue is suddenly destroyed, for instance by applying a 90° saturation RF pulse at the dissolved-phase resonance frequency, the only way for the dissolved-phase magnetization to return is for HXe atoms to leave the alveolar airspaces and enter the surrounding tissue. Thus, another way of assessing lung function through HXe MR spectroscopy is to quantify the rate at which the dissolved-phase HXe signal regrows after performing such an RF saturation. This approach has been referred to as xenon uptake spectroscopy,¹⁷ xenon interphase exchange spectroscopy²² or, most commonly, chemical shift saturation recovery (CSSR) spectroscopy^{23–25} and is discussed in more detail in this book in Chapter 19 by Muradyan and Patz.

While the basic CSSR technique is meant to quantify the rate at which fresh gas-phase HXe diffuses into the alveolar septum, by directly measuring the buildup of the dissolved-phase signal, the diffusive process is in fact bidirectional. The consequence of this circumstance is that RF pulses that selectively saturate dissolved-phase magnetization, after a short lag, also reduce the gas-phase magnetization, as some of the depolarized xenon atoms in the dissolved state pass back into the gas phase and are replaced by polarized xenon atoms from the gas phase.¹⁵ Thus, instead of measuring the dissolved phase signal, an alternative strategy for generating sensitivity to xenon exchange is to interrogate the gas-phase signal. This process is similar to magnetization transfer contrast (MTC) techniques used in conventional proton MRI, except that it is not complicated by T_1 relaxation-driven signal recovery.

The following procedure is an effective way to measure this “reverse” xenon diffusion.²⁶ First a gas-phase spectrum is acquired. Next a pair of narrow-band, *i.e.* chemical-shift selective, RF inversion pulses is applied, separated by a delay time τ . Both 180° RF pulses are centered at the dissolved phase resonance but have opposite RF phase. If desired, this step can be repeated to enhance the transfer weighting. Finally, a second gas-phase spectrum is acquired. In a static system (*i.e.*, no diffusion-driven exchange), the amplitude of the two gas-phase spectra would be identical except for signal losses due to inherent T_1 decay. However, if the dissolved-phase and gas-phase compartments stand in exchange with each other, then the gas-phase magnetization is reduced by polarized xenon atoms leaving the gas phase and by xenon atoms with inverted polarization entering the gas phase. The number of xenon atoms involved in this exchange process depends on the specifics of the global lung physiology, such as the surface-to-volume ratio, and the delay time τ . As τ increases, ever more xenon atoms with inverted polarization leave the dissolved phase until their pool has been depleted. At this point, ignoring the inherent T_1 , the total gas-phase depolarization would be proportional to the volume of the dissolved-phase compartment that exchanges with the gas-phase volume. The inherent T_1 can be determined separately, and subsequently corrected for, by shifting the RF inversion pulses to the other side of the gas resonance, *i.e.* from about

200 ppm to −200 ppm. Factors that contribute to the inherent T_1 include the actual T_1 relaxation of HXe in the presence of pulmonary oxygen, surface interactions, removal by the blood stream, and the impact of imperfect RF inversion pulses.

Using a simple one-dimensional diffusion model, the fractional gas-phase depolarization per RF pulse pair f_D as a function of the delay time τ can be described by

$$f_D(\tau) \propto \sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \left(1 - e^{-D_{\text{diss}}((2n-1)\pi/L)^2\tau} \right), \quad (18.1)$$

where L is the thickness of the alveolar wall and D_{diss} represents the xenon diffusion constant within the dissolved phase.²⁶ Further, for $\tau \gg L^2/(9D_{\text{diss}}\pi^2)$, eqn (18.1) simplifies to

$$f_D(\tau) \propto 1 - e^{-D_{\text{diss}}(\pi/L)^2\tau}. \quad (18.2)$$

Experimental results from rabbits indicate that for short delay times ($\tau < \sim 10$ ms), f_D increases rapidly with τ because the xenon atoms close to the surface can exchange quickly.²⁶ After about 20–30 ms all inverted xenon spins have either exchanged with the gas volume or are being removed from the gas exchange sites by the blood stream.

Due to conservation of mass, for small delay times and once a dynamic equilibrium between the gas- and dissolved-phase compartments has been established, the exchange spectroscopy techniques described here and the CSSR techniques described in Chapter 19 by Muradyan and Patz should yield complementary results. However, for longer delay times the contribution of xenon gas transport by the pulmonary blood stream becomes a major differentiating factor. While the CSSR technique detects all xenon dissolved in the lung parenchyma within the sensitive volume of the detection coil, exchange spectroscopy is only sensitive to that fraction of the dissolved xenon gas that returns to the alveolar air spaces after it has been exposed to one (and only one) of the two RF inversion pulses. As a consequence, by choosing appropriate parameters, both techniques assess a different pool of the HXe magnetization and provide different information about lung function. In particular, exchange spectroscopy characterizes mainly the static lung tissue within the immediate vicinity of the gas exchange sites while CSSR spectroscopy permits investigation of the entire dissolved-phase volume, and especially the dynamic gas transport component of the circulation.

18.3 Xenon Polarization Transfer Contrast (XTC) Imaging

By implementing imaging versions of the spectroscopic gas-exchange measurements described above, contrast can be generated in a gas-phase image that contains information about xenon exchange between the gas and dissolved phases. This technique is often referred to as xenon-polarization

transfer contrast (XTC) MRI. The quantification of regional pulmonary HXe gas exchange using XTC MRI was initially demonstrated in rabbits and dogs.^{15,26,27} However, only more recently litre quantities of highly polarized (>20%) xenon-129 have become available, and this significant advancement enabled Patz *et al.*^{23,24} to perform XTC imaging studies in humans for the first time.

The more recently developed multiple exchange-time XTC (MXTC)^{28,29} and single-breath XTC (SB-XTC)³⁰ MRI techniques extend the original XTC concept. The general design principles of the MXTC technique, which is based on a 3D gradient-echo (GRE) MR pulse sequence, are illustrated in Figure 18.2. Four sets of gas-phase HXe images (labeled I1, I2, I3, and I4) are acquired sequentially in the same breath hold. A series of N_1 frequency-selective saturation RF pulse pairs, each centered at -208 ppm relative to the gas phase, is applied between I1 and I2. Within each of these pairs, the first and second RF pulses have opposite phase and are separated in time by an adjustable delay τ_1 . A second series of saturation RF pulses, centered at $+208$ ppm but otherwise identical to the first set, is applied between I2 and I3. Finally, a third series of N_2 RF pulse pairs, also centered at $+208$ ppm but with different delay time τ_2 , is applied between I3 and I4. The image ratios $X1 = I3/I2$ and $X2 = I4/I3$ contain xenon exchange contrast, similar to the spectroscopic case described in Section 18.2, since the saturation RF pulses are applied at the dissolved-phase resonance frequency. The image ratio $I2/I1$ contains “control” contrast, since the RF pulses are applied far from the dissolved-phase resonance, and is used to correct the image ratios $I3/I2$ and $I4/I3$ for differences beyond the desired exchange contrast.

The ratio images $X1$ and $X2$, after normalization by the control ratio image, represent the regional gas-phase depolarization $f_D(\tau)$ at two different inter-pulse delay times τ_1 and τ_2 (Figure 18.2). By performing another breath-hold acquisition with two additional delay times τ_3 and τ_4 , a total of four $f_D(\tau)$ values can be measured at each pixel and then fitted to a model function, such as eqn (18.1), to yield maps of two characteristic lung parameters. The first is MXTC-F, the asymptotic value of $f_D(\tau)$, which represents gas-phase depolarization for an infinitely long delay time and is related to the overall volume of lung tissue in which the xenon is dissolved. The second is MXTC-S, defined as the square root of τ_C , the time constant with which the dissolved-phase magnetization is replenished. Within the same model used to derive eqn (18.1), it can further be shown that τ_C can be expressed as:

$$\tau_C = \frac{L^2}{D_{\text{diss}}\pi^2} \quad (18.3)$$

For a fixed xenon tissue diffusion constant D_{diss} ($D_{\text{diss}} = 3.3 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$)²⁶, MXTC-S is proportional to the functional septal wall thickness L . This functional wall thickness deviates from the physiological wall thickness since only tissue volumes containing xenon that directly exchange with the

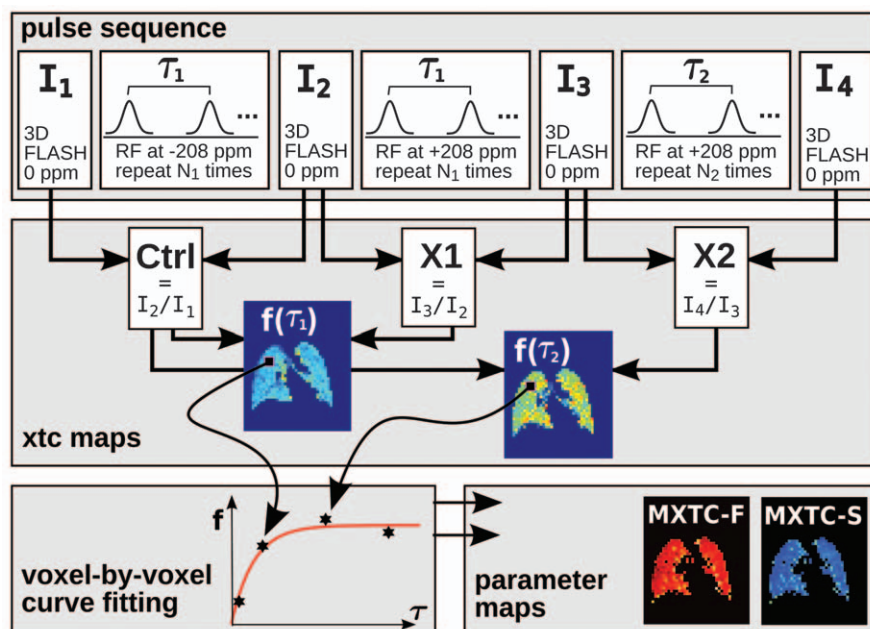


Figure 18.2 Schematic diagram of image acquisition and data analysis for the MXTC technique.

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alveolar gas phase during the contrast-generation period are assessed by this technique. Xenon that does not have the opportunity to exchange back into the air spaces, such as gas removed by the blood stream, is cancelled from the computational result by the normalization with the control ratio image.

In healthy volunteers, coronal maps of the MXTC-F and MXTC-S parameters are generally homogeneous in-plane but increase from anterior to posterior. This observation reflects the well-known gravitational compression of the lung in supine subjects. However, in asthmatics and patients with chronic obstructive pulmonary disease (COPD) the maps tend to be much more heterogeneous, revealing large regional changes in lung function induced by these diseases. In particular, MXTC-F maps of COPD patients exhibit areas of the lung with reduced gas exchange that are highly correlated with emphysematous regions detected by CT and apparent diffusion coefficient maps obtained from diffusion-weighted HXe MRI (Figure 18.3). Moreover, unlike the latter two techniques, the MXTC-S parameter maps provide information about the septal wall thickness that is not accessible otherwise. Thus, it is feasible to use MXTC MRI to distinguish changes in lung tissue density due to changes in alveolar diameter from those attributable to changes in septal wall thickness for instance caused by inflammatory processes.³¹

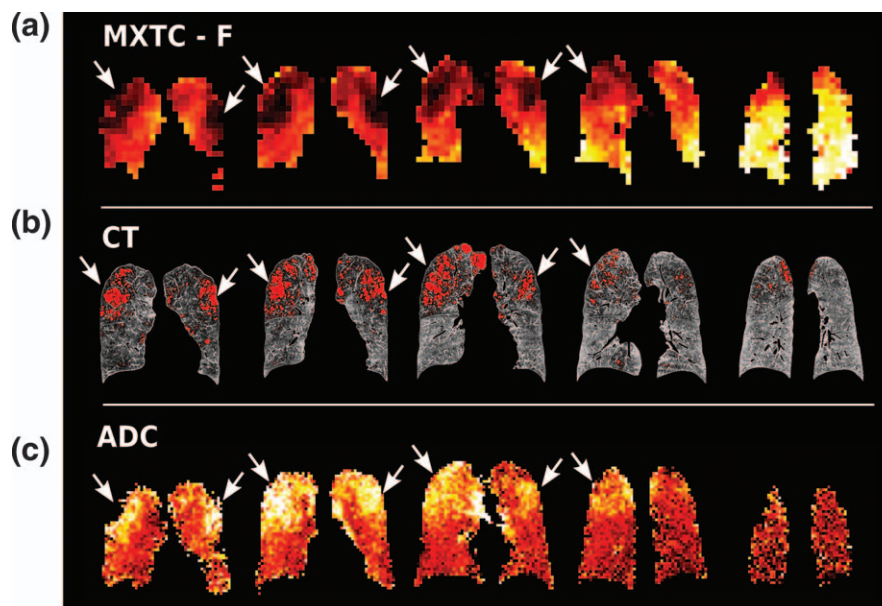


Figure 18.3 CT and HXe images of a COPD subject. The three different imaging techniques shown here depict emphysema in the same regions of the lung, as decreased parameter values in MXTC-F (a) and CT (b) (parameter values with less than -950 HU are colored in red) and increased parameter values in the apparent diffusion coefficient (ADC) map (c). Reprinted with permission from Dregely *et al.* (2011). Copyright 2011 Journal of Magnetic Resonance Imaging.

18.4 Chemical Shift Imaging (CSI)

The low xenon polarization levels available for the early studies performed in the 1990s made dissolved-phase imaging with meaningful spatial resolution largely infeasible. The main notable exception was the use of chemical shift imaging (CSI), a hybrid technique that combines low spatial-resolution imaging with MR spectroscopy. This fusion is achieved by collecting a free induction decay for every phase-encoded pixel (2D CSI) or voxel (3D CSI). The result is a data set with a dimensionality that is one greater than a conventional imaging data set. The advantage of such an approach is that a continuous frequency spectrum can be calculated at each encoded spatial location, revealing the different frequency components of the MR signal. By quantifying the area under each of the resonance peaks, a spatial distribution map for each spectral component can be calculated. The tradeoff is that the required scan time is much longer than a conventional imaging acquisition.

Using CSI methods, Swanson *et al.* were able to detect the accumulation of xenon-129 in the abdomen (most likely originating from the kidneys) and in the left ventricle of rats during inhalation of HXe.⁴ Employing the same

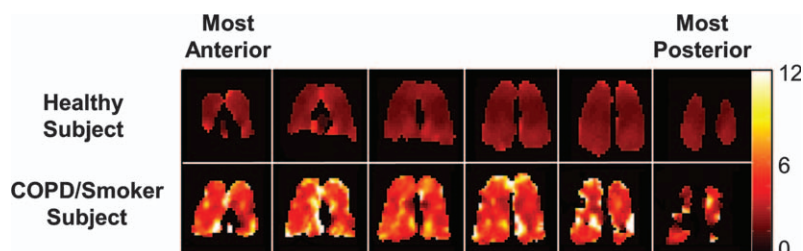


Figure 18.4 3D-CSI maps of the coronal TP-to-RBC ratio in a healthy subject and in a smoker with COPD.

technique, the group also obtained the first HXe MR dissolved-phase images in rat brains.³ More recently, Mazzanti *et al.*³² showed that the HXe distribution in the rat brain is affected by the regional brain activation level, similar to the well-known BOLD (blood-oxygen-level dependent) effect that forms the foundation for functional proton MRI.

Other researchers are currently investigating applications of HXe CSI in the lung. To achieve a scan time amenable to single breath-hold acquisition, and to optimize the use of the available HXe signal, Mata *et al.* employed short echo times (TE) of less than 2.1 milliseconds and an RF excitation flip angle of less than 30° , which allowed them to produce 2D and 3D-CSI maps of rabbit lungs with resolution, detail, and quality comparable to direct dissolved-phase imaging techniques.³³ In order to enhance the quantification and sensitivity of this method by more reliably differentiating the signal components originating from different physiologic lung compartments, the dissolved-phase resonance peaks were evaluated with principal component analysis.^{34–36} Using a similar 3D-CSI pulse sequence and post-processing analysis, Fernandes *et al.*³⁷ demonstrated in a population of eight subjects, that those with a history of significant exposure to cigarette smoke had higher TP-to-RBC ratio than healthy subjects. Further, a strong correlation of the TP-to-RBC ratio with FEV1/FVC ($R = 0.87$) was apparent, and the distribution of the TP-to-RBC ratios throughout the lung was found to be more heterogeneous in smokers than in healthy subjects (Figure 18.4).

18.5 Direct Dissolved-phase Xenon Imaging

Although CSI of inhaled HXe can provide simultaneous measurements of gas-phase xenon as well as xenon dissolved in lung tissue and blood, the relatively long acquisition time inherent to this imaging strategy limits the achievable spatial resolution during a breath-hold acquisition. CSI provides complete spectral decomposition over a continuum of possible resonant frequencies; however, the chemical shifts of the different frequency compartments in the lung are generally well known. Therefore, it is possible to improve imaging efficiency, while maintaining the ability to obtain useful chemical-shift contrast, by selectively imaging only certain frequencies of interest. This has been accomplished using a variety of different approaches,

most of which rely on either frequency-selective RF excitations or Dixon-like spectral decomposition strategies or both. Such approaches, combined with further improvements in xenon polarization technology,³⁸ have made it possible to perform direct dissolved-phase imaging in human subjects with useful spatial resolution and signal-to-noise ratio in a single breath-hold scan.

One approach for direct dissolved-phase imaging, first demonstrated by Muradyan *et al.* in human subjects,³⁹ is to use wide-bandwidth RF pulses to excite all gas-phase and dissolved-phase xenon resonances, and then use a 3-point Dixon method to decompose the received signal into separate gas-phase and dissolved-phase images. However, the gas-phase image will have much higher SNR than the dissolved-phase image using this approach, since the vast majority of HXe resides in the lung airspaces. If we are primarily interested in imaging xenon dissolved in the lung parenchyma, we can take advantage of the large chemical shift between the dissolved-phase and gas-phase resonances by applying RF excitation pulses centered on the dissolved-phase resonances, but with sufficiently narrow bandwidth to avoid exciting the gas-phase magnetization 200 ppm away. Because HXe in the airspaces acts as a reservoir that continually replenishes the dissolved-phase signal, the use of frequency-selective RF pulses makes much more efficient use of the available hyperpolarized magnetization, by minimizing the unnecessary depletion of this HXe signal reservoir.

Direct dissolved-phase imaging in the lung is further complicated by the existence of more than one frequency component in the dissolved-phase NMR spectrum. Although this feature makes it possible to distinguish xenon in tissue and plasma from xenon in red blood cells using phase-based spectral decomposition, which is discussed later in this section, it also leads to chemical-shift artifacts in ordinary dissolved-phase images obtained without using these techniques. Such artifacts arise from the fact that in a standard MR imaging pulse sequence the spatial origin of a signal is encoded as a frequency shift. Hence, the presence of two signal sources with different resonance frequencies will cause the two signals to appear at different positions in the resulting image, even when they originated at the same spatial location. This phenomenon also affects conventional MRI, in which there is often a spatial shift between fat and water-based tissues. The size of the shift depends on the readout bandwidth of the imaging pulse sequence.

A simple approach to sidestep the problem is to choose a sufficiently large readout bandwidth so that the spatial shift is smaller than a single imaging pixel. For instance, Wakayama *et al.* used a conventional gradient echo sequence with a 3.1 kHz per pixel bandwidth on a 9.4 T NMR spectrometer in a continuous HXe-flow configuration to image both HXe dissolved-phase components (tissue/plasma and red blood cells) in free-breathing mice without apparent chemical-shift image artifacts.^{40,41} In mice, the two dissolved-phase resonances are only separated by about 5 ppm (~ 560 Hz at 9.4 T), which is less than half the chemical shift observed in humans and therefore further helps in this regard. By also using a relatively low flip angle

(30°) and relatively long TR (100 ms) for the imaging pulse sequence, which avoids immediately saturating the HXe magnetization upon entering the dissolved phase, the resulting images showed dissolved-phase xenon as far downstream as the heart. Similarly, Cleveland *et al.* employed a 3D radial k-space trajectory to perform direct dissolved-phase imaging in humans during a single 16 s breath.⁴² Since with a radial trajectory the frequency difference manifests as blurring of the off-resonance species, the group used a high-bandwidth acquisition as well.

In what essentially amounts to a reverse approach for dealing with chemical-shift artifacts, Mugler *et al.* demonstrated the possibility of imaging dissolved-phase and gas-phase HXe simultaneously but separately, such that they appear side-by-side in the same image, by using a sufficiently small bandwidth and appropriately chosen spatial resolution.⁴³ Although the chemical shift between the two main dissolved-phase resonances is too small to separate using this approach, the shift between gas and dissolved phases is large enough to make this feasible. To achieve this feat for a chosen in-plane image resolution Δx , the receiver bandwidth BW has to obey

$$BW < \frac{\gamma B_0 \Delta\chi_{G-LP} \Delta x}{W_L}, \quad (18.4)$$

where γ is the gyromagnetic ratio for xenon-129, B_0 is the static magnetic field strength, $\Delta\chi_{G-LP}$ is the chemical shift difference between xenon-129 in the gas phase and xenon-129 dissolved in the lung parenchyma, and W_L is the width of the lung. At a bandwidth of 110 Hz per pixel and a frequency separation between the dissolved-phase and gas-phase resonances of about 3660 Hz at 1.5 T, the two signal sources will be depicted about 33 pixels apart. For a typical lung size of 240 mm and an in-plane image resolution of 10 mm, there will be no overlap between the gas and dissolved phase images. The tradeoff here is that at such a low bandwidth the two dissolved-phase resonances are offset by about 3 pixels, which gives the dissolved-phase image a slightly blurry appearance in the direction of the readout gradient.

Nevertheless, the advantage of this technique is that ventilation and dissolved-phase images are perfectly matched since they were acquired at exactly the same time, which permits the robust calculation of ratio maps from the two inherently co-registered image sets. Also, the HXe in the air-spaces acts as a reservoir that replenishes the dissolved-phase magnetization in an almost T_1 -like fashion between RF excitations.^{42,43} This allows the acquisition of 2D and 3D dissolved-phase image sets within a single breath hold. Initial findings indicated that the dissolved-phase and gas-phase images exhibited nonuniform signal distributions in subjects with lung disease (Figure 18.5). Further, the signal variations in the gas- and dissolved-phase images were similar, but not identical, possibly due to pathological alterations of lung tissue or regional blood flow.⁴³

While the methods discussed above combine all dissolved-phase signal sources into a single image, for many potential applications it is highly

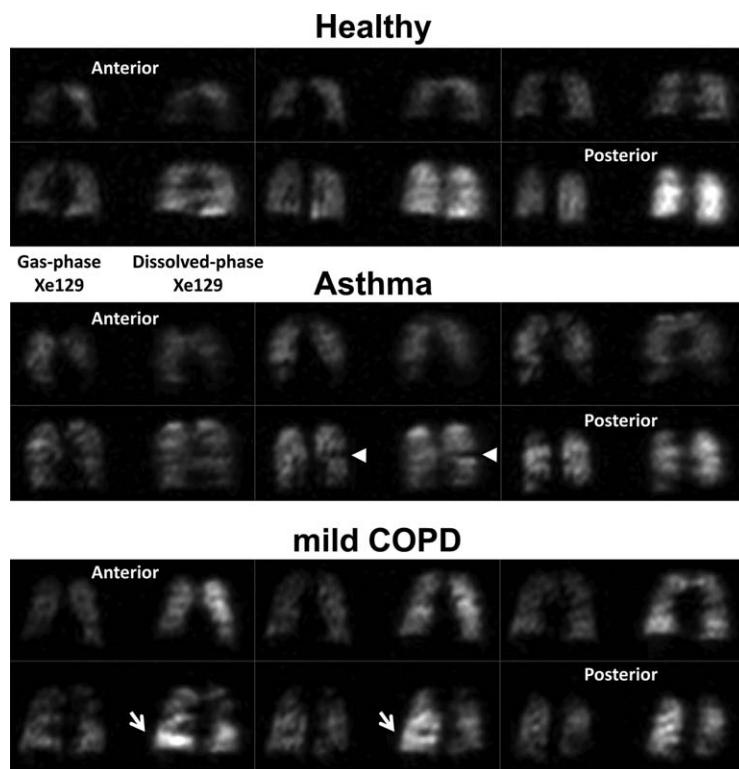


Figure 18.5 3D Coronal acquisitions of the whole lung in three subjects (healthy, asthma, and mild COPD) show marked spatial variations in ventilation and gas uptake in the subjects with asthma or COPD compared with generally uniform distributions in the healthy subject. Each panel shows the central six 20 mm-thick Xe-129 images from the respective acquisition. For the subject with asthma, arrowheads indicate signal dropout at the location of a ventilation defect; a band of elevated signal is seen just below this defect in the dissolved-phase component. For the subject with mild COPD, arrows indicate regions of elevated signal intensity in the dissolved-phase component. Reprinted with permission from Mugler *et al.* (2011). Copyright 2011 Proceedings of the National Academy of Sciences.

desirable to image the individual frequency components separately, since the different dissolved-phase peaks are associated with different physiological compartments in the lung. However, frequency-selective excitation of only one of the individual dissolved-phase resonances, while theoretically possible, would be difficult in practice due to the relatively small (20 ppm) chemical shift between the two primary dissolved-phase peaks in humans and the relatively short T_2^* (2–3 ms) of the dissolved-phase signals.

A more practically feasible approach is to fully excite both dissolved-phase resonances and employ a variant of the Dixon technique (which is commonly used for water–fat separation in proton MRI) to separate the two

dissolved-phase frequency components. Following an RF excitation centered between the dissolved-phase peaks, the two frequency components will precess with different angular velocities in the transverse plane. In the single-point Dixon technique, the echo time of the image acquisition is set so that the two signal components, whose frequency difference is known, will be exactly 90° out of phase at the chosen echo time. Under this arrangement, one signal component appears as the real part and the other appears as the imaginary part of the complex image. By incorporating this strategy into a 2D radial data acquisition, Driehuis *et al.* were able to generate separate images of the two dissolved-phase resonances.⁴⁴ Their method, referred to as xenon alveolar capillary transfer (XACT) imaging, permits a qualitative assessment of the rate with which HXe diffuses from the airspaces to the red blood cells.

Whereas in healthy alveoli the harmonic mean thickness of the barrier separating the alveolar airspaces from the capillary blood is only about $0.77\ \mu\text{m}$,⁴⁵ this thickness can increase considerably in inflammatory and fibrotic lung pathologies. As a result, diffusional gas transport from the airspaces to the red blood cells is impeded. By combining a rather large 90° RF excitation flip angle with a rather long TR of 50 ms, Driehuis *et al.* tuned the XACT sequence parameters such that barrier widths exceeding about $5\ \mu\text{m}$ should prevent fresh HXe from reaching the RBCs in time for image acquisition. This prediction was qualitatively validated in rats with unilateral bleomycin-induced interstitial lung fibrosis. In these animals it was shown that the RBC signal was almost completely absent in the injured lung (Figure 18.6). One drawback of the XACT technique is that like all implementations of the single-point Dixon method, it requires a high degree of field homogeneity across the lung to achieve a spatially identical phase for each of the two dissolved-phase resonances. Another drawback is the relatively long acquisition time to improve the image signal-to-noise ratio, which necessitates averaging over numerous breaths and makes application in its current form impractical for human subjects who are not mechanically ventilated.

More recently, Qing *et al.*⁴⁶ developed a method for 3D imaging of inhaled HXe which permits simultaneous, whole-lung mapping of gas-phase and dissolved-phase xenon-129 in a single breath hold, and which yields a quantitative measure of the fraction of xenon-129 dissolved in each of the two dissolved-phase compartments (tissue/plasma and RBCs). This method is based on a multi-echo 3D radial sequence which alternately excites the gas-phase and dissolved-phase resonances, collecting two echoes following each gas-phase excitation and three echoes following each dissolved-phase excitation. The magnitudes of the two gas-phase images provide a measure of regional ventilation and the phases are used to calculate a reference B_0 field map. This reference field map is then used as an initial estimate for the Hierarchical IDEAL method,⁴⁷ which was originally designed for water-fat separation but is used here to separately quantify the two dissolved-phase components based on the amplitude and phase of the three dissolved-phase images. The total acquisition time for this pulse sequence is around

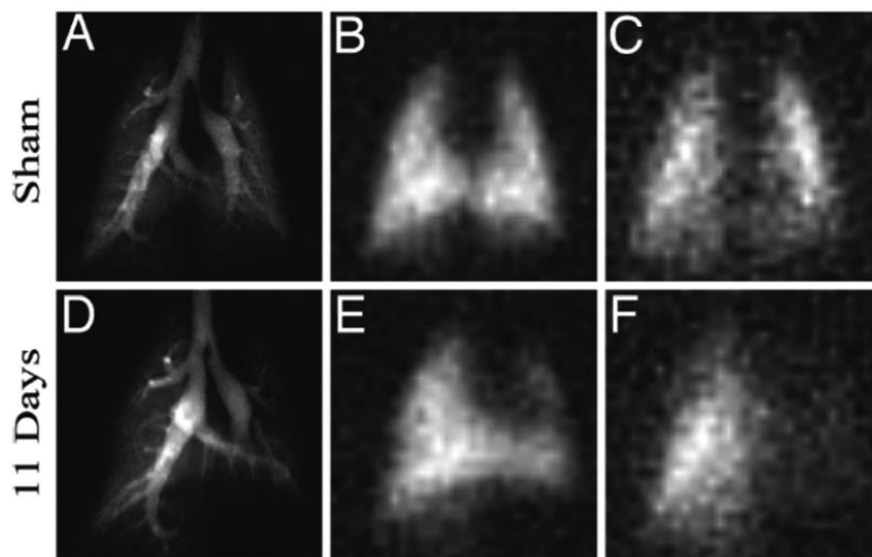


Figure 18.6 Comparison of HXe images in a sham left-lung instilled animal (A–C) vs. injured animal with left-lung fibrosis 11 days post instillation (D–F). (A) Airspace image in sham. (B) Barrier image in sham. (C) RBC image in sham. (D) Airspace image in injured animal. (E) Barrier image in injured animal. (F) RBC image in injured animal. Most notable is the nearly complete absence of xenon-RBC intensity in the injured left lung of the diseased animal (F), indicating that HXe does not reach the RBCs on the 50 ms image acquisition time scale, likely resulting from increased diffusion barrier thickness. However, note that the barrier images (B and E) closely match the corresponding airspace images (A and D).

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10 seconds, which is well tolerated by most subjects, providing 3D image sets with a spatial resolution of $7.6 \times 7.6 \times 17$ mm. Because the absolute size of the dissolved-phase signal has limited physiological relevance, four signal ratios are calculated to permit quantitative comparison among subjects: total dissolved-phase signal to gas-phase signal (DP-to-GP), tissue-to-gas (TP-to-GP), RBC-to-gas (RBC-to-GP), and RBC-to-tissue (RBC-to-TP).

A typical example from a 3D dissolved-phase imaging acquisition in healthy human subjects is shown in Figure 18.7 (columns labeled H), including xenon-129 gas-phase images, separate images of xenon-129 dissolved in lung tissue and RBCs, and corresponding TP-to-GP, RBC-to-GP, and RBC-to-TP ratio maps. The signal distribution in these images and ratio maps are generally uniform across each coronal slice but an anterior-to-posterior gradient can be observed in the TP-to-GP and RBC-to-GP ratio maps, which reflects the well-documented gravitational lung tissue compression in supine subjects.^{48–50} In contrast, marked differences can be

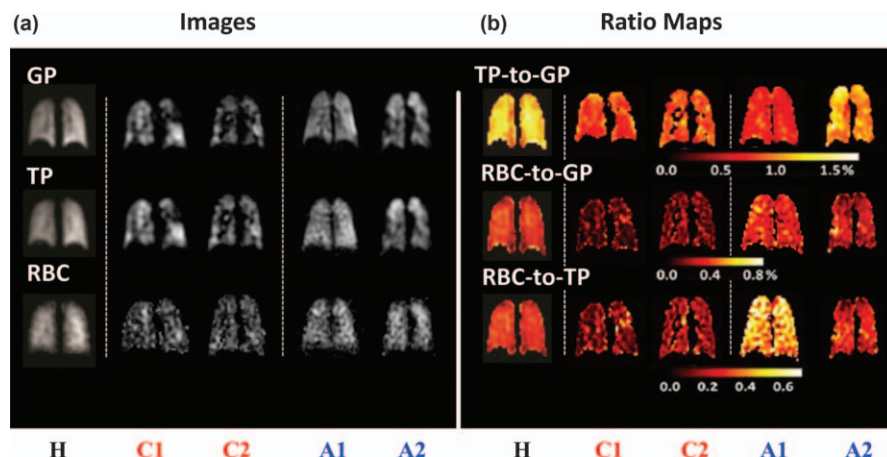


Figure 18.7 (a) Images of HXe lung ventilation and HXe dissolved in TP and RBC compartments. (b) Corresponding TP-to-GP, RBC-to-GP and RBC-to-TP ratio maps acquired in a healthy subject (H), two COPD subjects (C1 and C2), and two asthmatics (A1 and A2). The COPD subjects exhibited numerous ventilation defects and all xenon ratios were lower than those in healthy subjects. The results in asthmatics were less clean cut, with some ratios higher and others lower than in healthy subjects. Adapted with permission from Qing *et al.* (2014). Copyright 2014 Journal of Magnetic Resonance Imaging.

found in both the spatial distributions and relative fractions of the xenon-129 dissolved in tissue and RBCs for subjects with COPD (Figure 18.7, columns C1 and C2) and asthma (Figure 18.7, columns A1 and A2). For instance, numerous ventilation defects are evident in the GP ventilation images and the signal distribution in the ratio maps is not homogeneous. Also, the TP-to-GP, RBC-to-GP and RBC-to-TP ratios in the COPD subjects tend to be much lower than the mean values from healthy subjects. The findings in asthmatics are even more complex, with some patients having higher TP-to-GP, RBC-to-GP and RBC-to-TP ratios than typically found in healthy subjects and others having lower xenon ratios. However, the underlying physiological changes that lead to these findings are not understood. These results suggest that there is fertile ground for further physiological investigation of lung diseases using direct dissolved-phase imaging.

18.6 Conclusions

Unlike the XTC and MXTTC techniques, both 3D dissolved phase and CSI acquisitions directly image the dissolved-phase signal and can be used to generate separate maps of gas uptake by lung tissue and blood. CSSR spectroscopy, CSI, and 3D dissolved-phase imaging are all conceptually

similar techniques, but differ in the details of their implementation. A crucial distinction between CSSR spectroscopy and the others is that every TR window of the CSSR pulse sequence begins by saturating the dissolved-phase magnetization. As a result, at least in the ideal case, all spectroscopic acquisitions during a breath hold are completely independent from one another, and therefore the instantaneous HXe uptake by the lung parenchyma and the blood stream is assessed cleanly. In a 3D dissolved-phase or CSI acquisition, however, the flip angle of all RF pulses must be much lower than 90° , because exciting the dissolved phase with flip angles approaching 90° would quickly depolarize the gas-phase magnetization through exchange. Hence, the uptake measurement is not completely “reset” at each data acquisition as in the CSSR technique, and the resulting images reflect some sort of steady-state equilibrium that depends not only on physiological parameters such as the septal wall thickness and pulmonary blood flow, but also the flip angle and TR.⁵¹ However, the price to be paid for the more easily interpreted CSSR spectroscopy measurements is a lack of regional information. In addition, to prevent systematic differences when spectroscopic and imaging results are to be compared, care should be taken to flush HXe from the major airways before acquiring the spectroscopic data, since HXe in large airways does not participate in gas exchange. (Unwanted signal from the major airways can be excluded from image analysis but not from global spectroscopic measurements.)

As for any newly-developed set of techniques, many further refinements and many additional studies must be performed before lung function tests based on HXe gas uptake and exchange will become appropriate for clinical use. For instance, HXe dissolved-phase signal levels and associated ratios have been found to depend on lung inflation level.^{29,52} Thus a robust strategy for achieving a standardized lung inflation level across subjects, or else a robust strategy for retrospectively correcting for inflation level differences, will be necessary to obtain consistent results. Also, existing models of gas-exchange must be further refined to more closely tie the quantities measured by HXe MRI to the underlying lung physiology.^{53,54}

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CHAPTER 19

Xenon Septal Uptake

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19.1 Introduction

The main function of the lungs, gas exchange, is accomplished through diffusion processes driven by concentration gradients: after filling the lungs with air, oxygen diffuses into the lung parenchyma and blood, while carbon dioxide is driven from the blood out into the gas state, and exhaled. This is an efficient process since the surface area available for gas exchange is very large (on the order of 100 m²) and the gas–blood barrier is extremely thin (sometimes less than a micron). However, lung diseases decrease the efficiency of this process *via* different mechanisms. Therefore, any method that can evaluate the different sub-components of gas exchange will be valuable both in assessing the specific cause of any lung dysfunction and in evaluating efficacy of therapeutic intervention. Measurement of pulmonary septal uptake of hyperpolarized ¹²⁹Xe offers the opportunity to obtain such information on gas exchange. In addition, because it is a noninvasive method, it solves many problems associated with current morphologic methods that rely on fixation of tissue.

The invasive nature of lung preparation and fixation distorts the structure. For example, there are several methods to fix the lungs,^{1–4} each effective in highlighting different aspects of the morphology, *i.e.* fixation (i) by

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

instillation of fixative into the airways reveals the relationship between the tissue and the blood in capillaries, but cannot demonstrate the extracellular lining layer on the alveolar surface,⁵ while fixation (ii) by vascular perfusion preserves the extracellular lining but the relationship of capillary blood to tissue barrier cannot be revealed. Hence both fixation techniques need to be used to form a full picture of the structure. Morphologic data obtained from different fixation methods can also give different results. For example, Gil *et al.*⁶ studied the dependence of the alveolar surface area S on lung volume V . Lungs were filled either with air or saline to volumes between 40 and 100% of total lung capacity (TLC) and then fixed. Interestingly, S vs. V has a different functional form depending on the method of fixation: $S = kV^{0.33}$ for lungs fixed after air inflation vs. $S = kV^{0.58}$ for the lungs fixed by saline inflation. This difference is attributed to the profound influence interfacial tensions have on the structure of alveolar septa and surfaces. Moreover, the validity of the assumption that the structure and function of excised lungs mimic those of *in vivo* lungs has never been determined. In this light, the possibility of direct noninvasive *in vivo* studies is particularly important.

New diagnostic methods are also needed for clinical diagnosis. Traditional magnetic resonance imaging (MRI) measures the local density of protons *in vivo*. But due to the very low tissue content (the lung is primarily filled with air) compared to other organs, the lung is one of the most challenging organs to image with traditional MRI. Pulmonary function tests (PFTs) provide measurements such as Forced Expiratory Volume in 1 s (FEV_1), but lack disease specificity as they are not a measure of a specific pathology but rather of how the lung functions as a whole. Carbon monoxide diffusing capacity, D_{LCO} , while specifically measuring gas exchange, is also a global measurement and can be highly variable due to a dependence on blood volume. Computed tomography, CT, is the current imaging modality of choice for the lung as it provides very high spatial resolution maps of lung density. One metric provided by CT and used to quantify emphysema is the Low Area Attenuation percentage (LAA%). Unfortunately, there is poor correlation between LAA and quality of life measures.⁷

In addition to limited diagnostic measures available for the lung, pulmonary disease is a major public health issue. Indeed, Chronic Obstructive Pulmonary Disease (COPD) is the 4th leading cause of death in the world and the only major disease that is still on the rise. It affects nearly 65 million people worldwide.⁸ COPD is an airflow limiting disease with two main phenotypes: narrowing of the small airways (chronic bronchitis) and breakdown of the parenchymal tissue (emphysema). Both manifestations are almost always present to varying degrees. While CT can detect loss of septal tissue, the sensitivity of the method is poor; it typically takes 1–2 years before changes in a patient's condition can be measured with CT. In addition, both CT and nuclear medicine methods use ionizing radiation. Although CT does add some specificity by providing regional information, rather than measuring function, it quantifies tissue density. However, this may not unambiguously reflect the state of the disease; if both emphysema and

inflammation or fibrosis coexist, their effects on tissue density would negate each other and the pathology would not be visible on CT.

In addition to COPD, another pathology that would greatly benefit from detailed functional and morphological information is interstitial lung disease, which causes progressive scarring of lung tissue and thickening of the tissue barrier between gas and blood. All of these pathologies cause dyspnea and, if not treated, can progress and become debilitating.

It is at least in these two areas (morphological studies and diagnosis of disease) that hyperpolarized xenon (HPXe) MRI could significantly complement current capabilities. Its ability to noninvasively provide regional functional information without exposure to ionizing radiation is radically different from existing methods. As has already been described earlier in this book (see Chapter 2 by Jameson), xenon is lipophilic and readily dissolves into tissue and blood; due to its large polarizable electron cloud, it is extremely sensitive to its chemical environment and experiences a widely ranging chemical shift. For pulmonary MRI, this means observing separate peaks for (i) xenon residing in the gaseous phase in the airways and alveoli (G, assigned 0 ppm), (ii) xenon dissolved into tissue and blood plasma (TP, at ~ 197 ppm), and (iii) xenon dissolved into red blood cells (RBC, at ~ 217 ppm). This wide separation between gas and dissolved peaks allows one to study each phase separately. At high magnetic fields, the frequency difference due to the 20 ppm separation between RBC and TP is wide enough to distinguish them. As soon as the feasibility of dissolved state xenon measurements *in vivo* was demonstrated,^{9,10} it became clear that HPXe would be able to provide invaluable information about many aspects of lung morphology and function. Time-dependent NMR measurements of the diffusion of HPXe from alveolar gas spaces into septal tissue and blood offers a unique opportunity to non-invasively monitor gas exchange. To further obtain quantitative information about sub-components of gas exchange, several authors have developed simple mathematical models of xenon septal uptake. Fitting of the data obtained *in vivo* to these models allows one to obtain quantitative estimates of fundamental pulmonary parameters, such as the alveolar surface area per unit volume (S/V), the total thickness of the septal tissue (h), the thickness of the gas to blood barrier (δ) and blood transit time through gas exchange region (τ). Here we describe these analytical models developed over the last decade.^{11–17} We also describe many results obtained from these models in animals and humans.

19.2 Theoretical Treatment of Xenon Septal Uptake

19.2.1 Direct Measurements

Since xenon's presence in different environments gives rise to NMR signals at different frequencies, it opens a possibility to directly measure the signal from each environment separately. However, due to the small volume of the tissue and blood present within the lung, and a partition coefficient of only 0.1,

the collective dissolved state signal (both tissue and blood combined) is at most on the order of 2% of the gaseous signal. This has limited most of the direct measurements to spectroscopic whole lung approaches. Recently, there have been a few attempts to directly image the dissolved state, which are described in the next section.

All direct measurements that follow in this section are assumed to be spectroscopic unless stated otherwise. Most of them are based on the same experimental principle, commonly named Chemical Shift Saturation Recovery (CSSR). In CSSR, a selective RF pulse is initially applied to destroy the dissolved state xenon magnetization. This creates a step function in the xenon magnetization at the alveolar gas–tissue boundary: zero magnetization in the dissolved phase (M_D) and, due to the high gas diffusivity, relatively uniform magnetization in the gas phase (M_G). Recovery of the dissolved phase magnetization is then observed as a function of time allowed for diffusion of ^{129}Xe from alveolar gas spaces into tissue and blood.

In 2002, Butler *et al.*¹⁵ developed the 1st analytical model of HPXe diffusion into a porous medium that allowed quantification of its S/V . Note that V here refers to the gas volume and not the Euclidean volume of the sample. They demonstrated the technique on porous polyethylene phantoms by comparing the results with confocal microscopy measurements of the mean linear intercept L_m . Here the diffusion problem was solved for a semi-infinite slab. They defined a quantity F as the fraction of xenon magnetization initially in the gas phase that has diffused into the dissolved phase at time t :

$$F(t) = \frac{M_D(t)}{M_G(t=0)} \quad (19.1)$$

Ideally, the frequency selective saturation pulse is designed for maximal power deposition at the dissolved state frequency (90°) and a significantly smaller power deposition at the gas state frequency ($\sim 1^\circ$). In terms of the measured signal in the gas and dissolved phases S_G and S_D , respectively, one needs to correct for the flip angle differences; D is the xenon diffusivity in tissue

$$F(t) = \frac{M_D(t)}{M_G(t=0)} = \frac{S_D(t)}{S_G(t=0)} \frac{\sin(\alpha_G)}{\sin(\alpha_D)} \sim \frac{S}{V} \sqrt{\frac{4Dt}{\pi}} \quad (19.2)$$

The semi-infinite theoretical 1D model is valid as long as the polyethylene is not saturated with Xe, *i.e.* diffusion is limited by the surface area. In practice, this means measuring $F(t)$ for diffusion times that are short compared to the time to diffuse across the polyethylene slab.

More sophisticated models are required to address a finite thickness slab and flowing blood. Månsson *et al.*¹¹ modeled the gas exchange using a three-compartment model with spherical symmetry, where gaseous xenon diffuses from alveolus through the tissue compartment into the blood and is then carried away from the capillary compartment. Figure 19.1A shows the

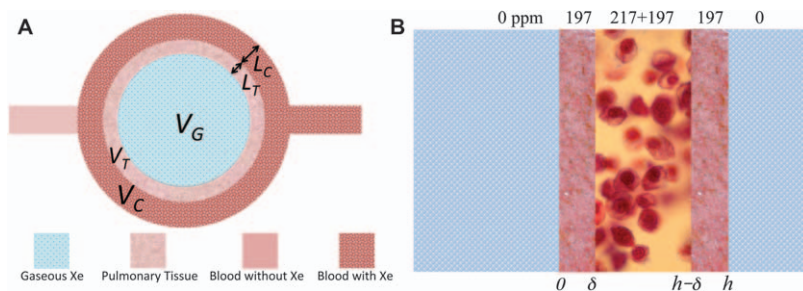


Figure 19.1 Schematics for different xenon uptake models. A – A three compartment alveolar model with spherical symmetry used by Månsson *et al.*¹¹ In this model xenon gas diffuses from the alveolar gas space through a tissue and a capillary compartments and is transported away by the blood from the capillary compartment. Here L_T is the tissue thickness, L_C is the capillary compartment thickness, V_G is the alveolar gas volume, V_T is the tissue volume, V_C is the capillary volume around a single alveolus. B – A compartmental alveolar model used by Driehuys *et al.*,¹³ Patz *et al.*¹⁶ and Chang.¹⁷ Patz *et al.* treated tissue and blood as a single compartment; while Driehuys *et al.* and Chang used a three-compartment model, separating the tissue and the blood plasma from the red blood cells. Here a pulmonary tissue slab of thickness δ is padded by pulmonary capillary from one side and alveolar gas from the other. The total gas–blood barrier thickness is h . Upon inhalation, the xenon dissolves from gaseous alveolar space (blue part on the edges of the schematic) through the lung parenchyma into the capillary bed, from where it is carried away by the blood. If the gaseous xenon is used as a chemical shift reference (set at 0 ppm, see top of the schematic), then the signal from the xenon dissolved into the tissue and the blood plasma will be 197 ppm away, while signal from xenon dissolved in the red blood cells will be 217 ppm away.

geometry for which the problem was solved. A 1D diffusion model describing the kinetics of the process was proposed. Assuming that the partition coefficient between tissue and blood is 1, and the alveoli are spherical, a solution in the form of an infinite series for both tissue and capillary compartments was obtained. They further separated the signal from the capillary compartment into plasma and RBC signals and obtained equations governing the dynamics of xenon in the tissue and plasma (TP) and in RBC separately:

$$S_{RBC}(t) = S_{RBC0} \left(1 + \sum_{n=1}^{\infty} c_{RBCn} e^{-t/\tau_n} \right) + S_{RBC1} t, \quad (19.3)$$

$$S_{TP}(t) = S_{TP0} \left(1 + \sum_{n=1}^{\infty} c_{TPn} e^{-t/\tau_n} \right) + S_{TP1} t$$

where the parameters S_{TP0} , S_{TP1} and S_{RBC0} , S_{RBC1} represent the intercepts and slopes of the asymptotes of the tissue-plasma and blood signals,

respectively. To limit the number of fitting parameters with a finite data set, they used only the 1st term in the series with $C_{RBC_1} = C_{TP_1} = -1$. This results in:

$$\begin{aligned} S_{RBC}(t) &= S_{RBC_0} \left(1 - e^{-t/\tau_1}\right) + S_{RBC_1} t, \\ S_{TP}(t) &= S_{TP_0} \left(1 - e^{-t/\tau_1}\right) + S_{TP_1} t \end{aligned} \quad (19.4)$$

From this set of parameters (S_{TP_0} , S_{TP_1} , S_{RBC_0} , S_{RBC_1}) they calculated tissue barrier thickness δ , average diffusion length through capillary L_C , lung perfusion Q , mean transit time τ , and hematocrit H .

Another approach was proposed by Driehuys *et al.*,¹³ who also considered 1D diffusion problem for a three-compartment model for a tissue/blood slab (see Figure 19.1B). They wrote the solution to the diffusion equation in terms of a sum of exponents, represented by the integral of error function complement *ierfc*. Similar to Månsson *et al.*, they separated the contributions from tissue-plasma S_{TP} and RBC S_{RBC} using the hematocrit H :

$$\begin{aligned} \frac{S_{RBC}(t)}{S_0} &= \frac{4\lambda H \sqrt{Dt}}{L_A} \sum_{n=0}^{\infty} (-1)^n \left[\text{ierfc} \left(\frac{(2n+1)L - L_C}{2\sqrt{Dt}} \right) - \text{ierf} \left(\frac{(2n+1)L + L_C}{2\sqrt{Dt}} \right) \right], \\ \frac{S_{TP}(t)}{S_0} &= \left[\frac{4\lambda \sqrt{Dt}}{L_A} \sum_{n=0}^{\infty} (-1)^n \left[\text{ierfc} \left(\frac{(2n+1)L - L}{2\sqrt{Dt}} \right) - \text{ierf} \left(\frac{(2n+1)L + L}{2\sqrt{Dt}} \right) \right] \right] \\ &\quad - \frac{S_{RBC}(t)}{S_0} \end{aligned} \quad (19.5)$$

Here λ is the solubility of xenon in tissue, D is the dissolved phase diffusion coefficient, S_0 is the gas state signal, L_A is the linear dimension of an alveolus.

After validation of CSSR's ability to measure S/V by Butler *et al.*, it was used to study lungs *in vivo*.^{18,19} The theory was also modified to be valid for all diffusion times in a finite slab.¹⁶ To incorporate blood flow into this model, we first assumed that ¹²⁹Xe diffuses directly into the blood, orthogonally to the direction of its flow and without having to cross a layer of parenchyma. Also for simplicity we assumed plug flow. Figure 19.2A demonstrates the simplified geometry for which the diffusion equation is solved. In this treatment, we first used separation of variables to obtain the solution to the diffusion equation in the absence of the blood flow. Within the time interval $[0, t]$, allowed for diffusion, a segment of the blood that was just upstream of the gas exchange region (GER) prior to the start of diffusion (region R1, see Figure 19.2B) will make its way into the GER. If $t \geq \tau$, then at time t , R1 will occupy the whole GER. For shorter t 's, however, there will be another segment R2, that will spend the entire time from 0 to t inside the GER.

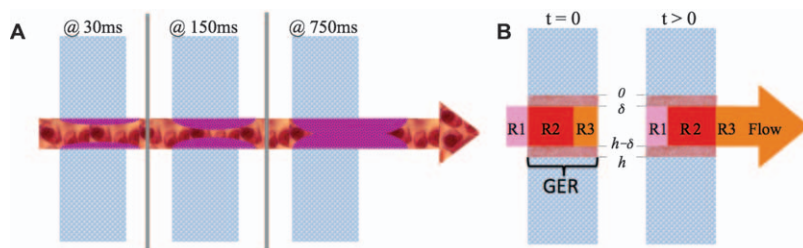


Figure 19.2 A schematic for CSSR and MOXE models (originally described in ref. 16). A – cross-sectional schematic of the xenon uptake by the tissue/blood at different diffusion times. In this figure light blue depicts xenon in gaseous state, while purple represents dissolved state xenon. B – Position of three spatially distinct regions of blood flow, labeled R1, R2 and R3 at times $t = 0$ and $t > 0$. The distance the blood travels in time t is $Dx = vt$. Blood in regions R1 and R3 experience gas exchange for only a fraction of the time t , whereas region R2 experiences gas exchange for the entire time t . Note that blood in region R1 on the left and in region R3 on the right correspond to blood in the pulmonary arterioles and venules and are therefore both located physically within the lung, although outside of the gas exchange region (GER in the schematic, R2 and R3 at $t = 0$, and R1 and R2 at $t > 0$). Since we observe xenon within the lung, xenon diffusing into the blood within the gas exchange region and afterwards traveling downstream into the venules is observed as part of the xenon septal uptake data.

Finally, at time 0 the space between R2 and the right edge of the GER (Figure 19.2B) will contain R3: a segment that will completely exit the GER at time t . If v is the velocity of the blood flow, then both R1 and R3 are of length vt , hence $R1 + R2$ is of the same length as $R2 + R3$, and both are equal to the total length of GER.

Since the entire R2 is involved in the diffusion between 0 and t , for R2, the fraction of the septal thickness containing ^{129}Xe (the distance of ^{129}Xe 's diffusion into the segment) will be uniform over its length. The fraction of the alveolar surface area associated with R2 is $(\tau - t)/\tau$, where τ is the capillary transit time. By contrast, some parts of R1 and R3 move respectively in and out of the GER, causing the fractions of septal thickness containing ^{129}Xe to change along their lengths. In this case the average fractions have to be calculated by integrating septal thickness over the diffusion time. The fraction of the surface associated with both R1 and R3 is t/τ . By combining the three contributions, the total fraction of ^{129}Xe is calculated. With the appropriately chosen boundary and initial conditions, and the blood flow treated as described above, the dissolved state signal can be expressed as follows:

$$F(t) = F_0 + \frac{\lambda h S}{2 V} \left(\frac{\tau - t}{\tau} \right) f \left(\frac{Dt}{h^2} \right) + \lambda h \frac{S}{V} \left[\frac{t}{\tau} + \frac{8h^2}{D\pi^4} \frac{1}{\tau} \cdot g \left(\frac{Dt}{h^2} \right) \right], \quad (19.6)$$

where λ is xenon tissue solubility constant, h is the septal thickness, D is the dissolved state diffusion coefficient, τ is the blood transit time through the gas exchange region, and functions f and g are defined as

$$\begin{aligned} f\left(\frac{Dt}{h^2}\right) &= \left[1 - \sum_{n, \text{ odd}} \frac{8}{\pi^2 n^2} \exp\left(-Dt\left(\frac{\pi n}{h}\right)^2\right)\right], \\ g\left(\frac{Dt}{h^2}\right) &= \left[\sum_{n, \text{ odd}} \frac{1}{n^4} \left\{\exp\left(-Dt\left(\frac{\pi n}{h}\right)^2\right) - 1\right\}\right]. \end{aligned} \quad (19.7)$$

F_0 in eqn (19.6) represents an offset associated with either an imperfect saturation of the dissolved phase and/or structures sufficiently thin that they saturate earlier than our measurement time window.

Chang¹⁷ extended the CSSR model to separate the contributions of the tissue and blood plasma from that of the RBC. The geometry they considered is similar to that used for the treatment of the problem by Driehuys *et al.* and Patz *et al.* (see Figure 19.1B). To calculate the signal from the tissue, they integrated the solution to the CSSR problem by Patz *et al.*¹⁶ in the absence of the blood flow over the tissue region: from 0 to δ and from $h - \delta$ to h . To calculate the contribution from the blood compartment, Chang also treats the blood flow similar to Patz *et al.*¹⁶ Further, Chang defines η as the fraction of RBC in blood and separates the signals from RBC and plasma, while combining plasma and tissue signals together:

$$\begin{aligned} S_{\text{RBC}}(t) &= \eta \frac{\lambda h S}{2 V} \left\{ 2 \left[\left(1 - \frac{2\delta}{h}\right) \frac{t}{\tau} - \frac{8T}{\pi^2 \tau} \sum_{n=\text{odd}} \frac{1}{n^4} \cos\left(\frac{n\pi\delta}{h}\right) \left(1 - \exp\left(-\frac{n^2 t}{T}\right)\right) \right] \right. \\ &\quad \left. + \left(1 - \frac{t}{\tau}\right) \left[\left(1 - \frac{2\delta}{h}\right) - \frac{8}{\pi^2} \sum_{n=\text{odd}} \frac{1}{n^2} \cos\left(\frac{n\pi\delta}{h}\right) \exp\left(-\frac{n^2 t}{T}\right) \right] \right\}, \end{aligned} \quad (19.8A)$$

and

$$\begin{aligned} S_{\text{TP}}(t) &= \frac{\lambda h S}{2 V} \left[\frac{2\delta}{h} - \frac{8}{\pi^2} \sum_{n=\text{odd}} \frac{1}{n^2} \left(1 - \cos\left(\frac{n\pi\delta}{h}\right)\right) \exp\left(-\frac{n^2 t}{T}\right) \right] \\ &\quad + (1 - \eta) \frac{\lambda h S}{2 V} \left\{ 2 \left[\left(1 - \frac{2\delta}{h}\right) \frac{t}{\tau} - \frac{8T}{\pi^2 \tau} \sum_{n=\text{odd}} \frac{1}{n^4} \cos\left(\frac{n\pi\delta}{h}\right) \left(1 - \exp\left(-\frac{n^2 t}{T}\right)\right) \right] \right. \\ &\quad \left. + \left(1 - \frac{t}{\tau}\right) \left[\left(1 - \frac{2\delta}{h}\right) - \frac{8}{\pi^2} \sum_{n=\text{odd}} \frac{1}{n^2} \cos\left(\frac{n\pi\delta}{h}\right) \exp\left(-\frac{n^2 t}{T}\right) \right] \right\}, \end{aligned} \quad (19.8B)$$

where $T = h^2/\pi^2 D$ is the exchange time constant in the lung, D is the diffusion coefficient of dissolved xenon, λ is the Ostwald solubility of xenon in lung

parenchyma, δ/h is so called barrier-to-septum ratio, and τ is the pulmonary capillary transit time. Finally, using solubility in RBC λ_{RBC} and plasma λ_{P} , hematocrit is calculated:

$$H = \frac{\eta/\lambda_{\text{RBC}}}{\eta/\lambda_{\text{RBC}} + (1 - \eta)/\lambda_{\text{P}}} \quad (19.9)$$

19.2.2 Indirect Measurements

Ruppert *et al.*¹⁴ approached the problem from another angle. Instead of measuring a low SNR dissolved state magnetization, they considered what the effect of its inversion would be on the gas state. They implemented the Xenon polarization Transfer Contrast (XTC) technique, where the gas magnetization is measured before and after multiple consecutive applications of spectrally selective inversion (180°) pulses at the dissolved state frequency (~ 200 ppm) separated by a diffusion time. They also considered the simplified 1D diffusion model and solved the equation for a finite slab. They derived the dissolved state signal after application of the inversion pulse at time zero as

$$I_{\text{D}}(t) \propto \lambda C_{\text{a}} h - \sum_{n=1}^{\infty} \frac{16\lambda C_{\text{a}} h}{((2n-1)\pi)^2} \exp\left(-D\left(\frac{(2n-1)\pi}{h}\right)^2 t\right) \quad (19.10)$$

where C_{a} is the alveolar concentration of the HPXe, λ is again the solubility of the xenon in tissue, h is the thickness of the dissolved state region, and D is the diffusion constant of the dissolved state xenon. They calculated the change in the gas state signal (S_{G}) due to inversion of the dissolved state magnetization and the diffusion of the uninverted gaseous xenon into the tissue:

$$\frac{S_{\text{G}}(t)}{S_{\text{G}}(0)} = 1 + \frac{S_{\text{D}}(0) - S_{\text{D}}(t)}{S_{\text{G}}(0)} = 1 - f_{\text{D}}(t) \quad (19.11)$$

In order to account for other signal decay mechanisms, such as RF depletion of the gas state magnetization and T_1 relaxation during the inversion and diffusion times, they also performed a “control” experiment, where everything but the frequency of the selective inversion pulse was kept the same. The frequency of the inversion pulse in the control experiment was set to -200 ppm, so that the effect of the RF pulse would be the same on the gas state, while leaving the dissolved state magnetization intact. With all the corrections accounted for, after application of N inversion pulses they demonstrated that

$$f_{\text{D}} = 1 - \sqrt[N]{\frac{S_{\text{XTC,After}}/S_{\text{XTC,Before}}}{S_{\text{Control,After}}/S_{\text{Control,Before}}}} \quad (19.12)$$

and that for long diffusion times ($\gg h^2/(D\pi^2)$) $f_{\text{D}} \rightarrow \frac{2N\lambda V_{\text{D}}}{V_{\text{G}}}$, where V_{G} and V_{D} are volumes of the alveoli and alveolar membranes, respectively. The ability to indirectly observe lung function through measurement of the

higher SNR gas state signal opened new opportunities for regional functional measurements. It is worth mentioning that f_D measured with XTC is not equivalent to the fractional gas transport F measured with the CSSR technique.^{19–21} The reason is that XTC with inversion pulses involves diffusion of xenon magnetization both from alveolar gas spaces to septal tissue and the reverse. However, the reverse diffusion from blood to alveolar gas spaces can only take place when the blood is in the gas exchange region. Therefore, there are two fundamentally different dependencies determined by whether or not blood remains in the gas exchange region during the diffusion time. CSSR, however, only involves diffusion in one direction: from gas to tissue. The only case when f_D and F are equivalent is when a 90° saturation pulse is used for the XTC generation.

19.3 Spectroscopy of the Dissolved State – Xenon Uptake Curve

There is a significant body of spectroscopic work done to study the whole lung xenon uptake curve in both, animal models and humans. In what follows we will review the results using different theoretical approaches.

Månsson *et al.*¹¹ studied naive rats and rats with acute inflammatory lung injury caused by instillation of lipopolysaccharide (LPS). They observed significant differences in total diffusion length, capillary diffusion length, and hematocrit between the control and the LPS-treated group. However, no significant difference in tissue thickness, mean transit time, relative blood volume or perfusion was detected.

Driehuys *et al.*¹³ studied the xenon uptake curve in control rats and rats with interstitial fibrosis induced by unilateral instillation of bleomycin. They used a CSSR-type spectroscopic technique with 12 different diffusion times ranging between 11 and 200 ms to obtain the dynamic xenon uptake curve for TP and RBC, separately, and fit the data to the equation (19.5). Although they observed no change in the shape of the uptake curve between control and treated animals, there was a significant drop in the ratio of saturation RBC signal to TP signal in the injured animals ($RBC/TP = 0.69 \pm 0.12$, from 9 injured rats) compared to the controls ($RBC/TP = 0.87 \pm 0.14$, from 5 control rats).

Abdeen *et al.*¹² utilized measurements of xenon diffusion into septal tissue and gas phase imaging to measure lung volume and gas transfer constants. Combining these with measured end inspiratory pressure during a breath-hold experiment, they obtained the diffusing capacity of xenon for lung parenchyma and RBCs.

Chang *et al.*²² analyzed the xenon uptake data using MOXE, an extension to the CSSR approach to separate TP and RBC contributions to the dissolved state signal. They fit existing data from 10 healthy volunteers (diffusion times were between 4 and 900 ms) to eqn (19.8A) and (19.8B) to obtain values for S/V , total septal wall thickness d , air–blood barrier thickness δ , and blood transit time τ

using values of $\lambda=0.2$,²³ and $D=3.3\times10^{-6}\text{ cm}^2\text{ s}^{-1}$.¹⁴ They calculated hematocrit H using eqn (19.9). The results and their comparison to the literature values^{24–27} are presented in Table 19.1. The values of S/V , d and τ agreed with literature values, while δ was higher and H was lower than the reported values. They note that the discrepancy in δ could stem from the inability to fully saturate the dissolved state signal – due to power limitations on the MRI systems they used, the “saturation” pulses were limited to flip angles of either 80° or 70° . Another source of error is the non-uniform B_1 field within the coil, which also affects the “saturation” pulse distribution within the lung.

Our group has studied 4 healthy volunteers, two subjects with mild and moderate COPD and two subjects with Interstitial Lung Disease (ILD). We used CSSR with 13 different diffusion times ranging from 17 ms to 1s to obtain a xenon uptake curve (Figure 19.3). Data were acquired at three

Table 19.1 Pulmonary parameters obtained from a xenon uptake curve using the MOXE model, and their comparison to the other reported values from literature.

Parameter	MOXE	Literature
$S/V/\text{cm}^{-1}$	210 ± 50	250
$h/\mu\text{m}$	9.2 ± 6.5	10
$\delta/\mu\text{m}$	1.0 ± 0.3	0.6
$H\text{ [\%]}$	27 ± 50	46
τ/s	1.6 ± 0.3	1.6

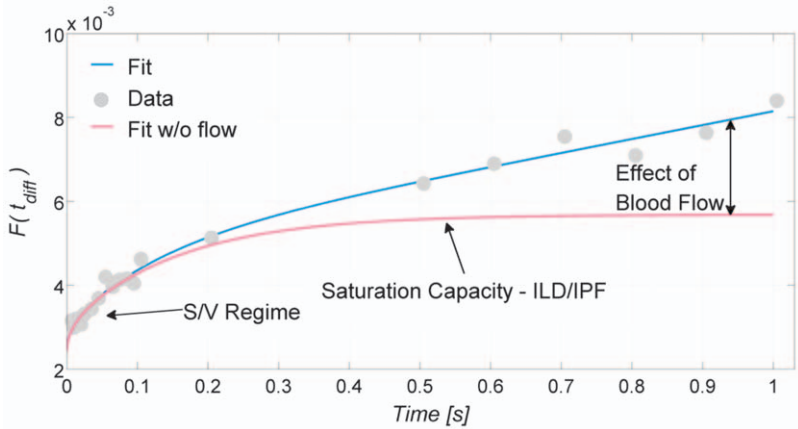


Figure 19.3 Example of $F(t)$ data plotted *versus* time. The data here are from one of the subjects with COPD (Gold Stage 1), whose data were summarized in ref. 16. Also shown is the fit to the CSSR theoretical expression (blue curve). Using the fitted parameters S/V and h obtained for the blue curve, but setting $t \rightarrow \infty$, a separate curve was plotted (red curve) that shows the behavior for no blood flow. Note that the dissolved state data were corrected for T_1 decay during the diffusion time t .

different lung volumes for healthy subjects and at a single volume for those with lung disease. For a proper comparison between individuals, lung volumes (LV) were normalized to their respective total lung capacities (TLC). Using the finite slab model accounting for blood flow, we fitted the data to eqn (19.6) with literature values for $\lambda = 0.1$ and $D = 3 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$.¹⁴ The obtained S/V , h and τ values are summarized in Figure 19.4. There are some features to note. Despite the use of a simple analytical model, the values for the parenchymal thickness are remarkably similar to those measured with histology on fixed lungs.²⁵ Also, the values obtained for blood transit time τ are $\sim 1.5 \text{ s}$ and very similar to the range of the values (mean 1.6 s , median 1.2 s , with a wide spread) reported in the literature.²⁶ However, when comparing our S/V estimates to literature values from fixed lung histology,²⁵ we found that our values were $\sim 40\%$ lower. A possible explanation is that the lower bound on our diffusion time window was 17 ms . Thus, thinner sections of septal tissue between capillaries may have already been saturated after 17 ms . The diffusion distance in septal tissue in 17 ms is $\delta \approx \sqrt{2Dt} = 3.2 \mu\text{m}$, which is large enough to saturate thinner sections. This could also explain the need for the term F_0 .

For the two ILD subjects, the S/V values fall within the same range as for healthy subjects, consistent with a lack of parenchymally destructive disease. COPD subjects, however, show a striking loss of S/V , as one would expect with an emphysematous disease. On the other hand, the patients with ILD have values of h 36% and 97% larger than the mean value of the healthy volunteers at TLC, consistent with laying down of excess connective tissue and increased interstitial fluid in progressive fibrotic diseases, while COPD subjects show no significant deviation of h from healthy volunteers. Values for the capillary transit time are fairly constant as a function of normalized lung volume but exhibit relatively high variability. The two ILD patients do not show a significant difference in transit times compared to healthy subjects; COPD subjects do show decreased values of τ although these values are still within the error bar of the healthy volunteers.

There are several other measurements performed on patients with Interstitial Pulmonary Fibrosis (IPF), which is a subset of ILD. Liljeroth *et al.*²⁸ reported elevated RBC/TP ratios in an IPF patient compared to healthy subjects. She also looked at the reproducibility of the measurements in the same subjects separated by several months and reported a reproducibility of $\sim 5.6\%$ in healthy and 1.2% in the IPF subject. Kaushik *et al.*²⁹ reported a 3-fold reduction in mean RBC/TP values measured in 5 IPF subjects (0.15 ± 0.04) compared to the mean value from 10 healthy volunteers (0.55 ± 0.13). Using a gas-phase signal to normalize values, they determined that the RBC signal was reduced by a factor of 2.3, while the TP signal had increased by a factor of 1.4. They also reported on excellent correlation between RBC/TP and D_{LCO} .

Stewart *et al.*³⁰ recently reported on xenon uptake measurements in healthy volunteers, subjects with IPF and systemic sclerosis (SSc). They used

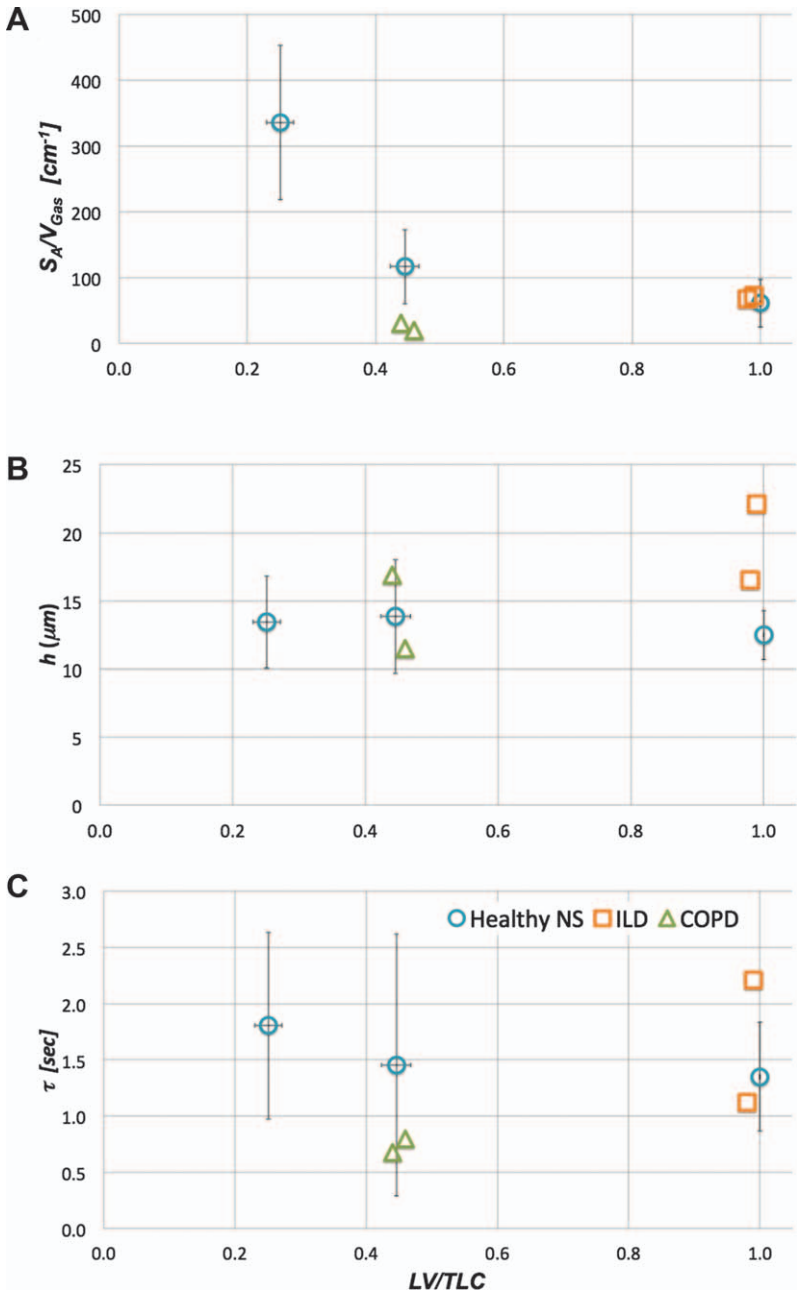


Figure 19.4 Results of data analysis for (A) S/V , (B) h and (C) τ as a function of lung volume normalized to TLC using CSSR model.¹⁶ The results are shown for four healthy subjects, two subjects with mild ILD and two subjects with COPD, one with mild and one with mild/moderate disease.

the CSSR approach to collect xenon uptake data for diffusion times ranging from 20 ms to 1 s. They fit their data to the analytical models of Månsson's,¹¹ CSSR¹⁶ and MOXE¹⁷ and compared the results. They showed that signal at TP is increased, while that at RBC is decreased in disease compared to healthy volunteers, indicating impaired and delayed gas transfer to blood in the patients, most probably due to inflammation and thickening of lung tissue (Figure 19.5). They noted that a correlation between the capillary transit time obtained from xenon uptake and the pulmonary transit time obtained from DCE-MRI was the strongest when the CSSR model¹⁶ was used to fit the data.

Imai *et al.*³¹ measured the xenon septal uptake in 6 control and 6 elastase treated mice at 9.4 T using CSSR and fit their data to our analytical formula for slab diffusion.³² A significant reduction in V_D/V_G ($V_D = Sh$) was seen in the elastase treated animals and verified by histological measurements

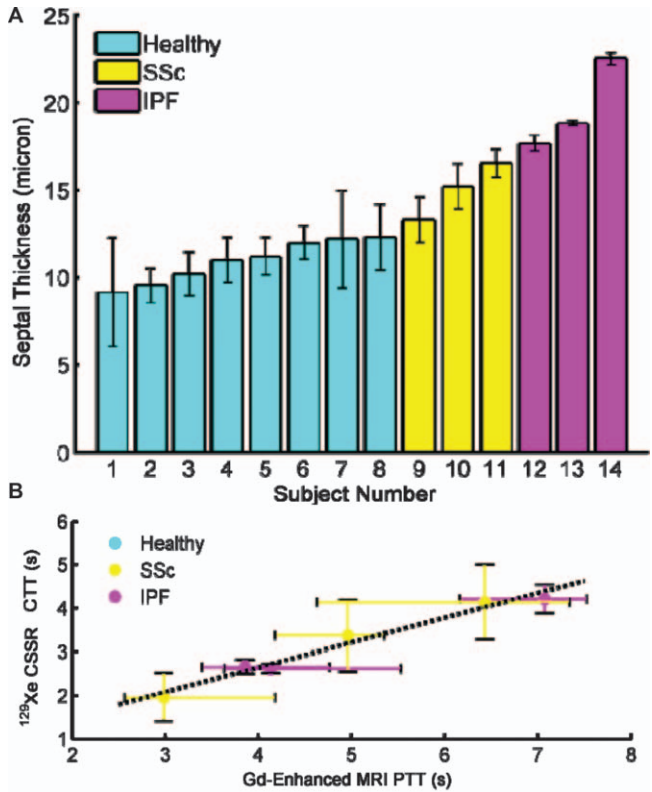


Figure 19.5 Data from Stewart *et al.*³⁰ A – Mean alveolar septal thicknesses for healthy volunteers and subjects with IPF and SSc, as derived from the CSSR model, displayed in order of increasing thickness. B – Xe CSSR derived capillary transit time (CTT) correlation with whole lung pulmonary transit time (PTT) obtained from DCE-MRI.

of the mean linear intercept L_m . They observed an anticipated reduction in V_D/V_G in the elastase treated animals, and a strikingly good agreement between V_D/V_G measured with CSSR and histology. No significant changes were seen between controls and treated animals for either the mean h ($\sim 6.2 \mu\text{m}$), or τ ($\sim 0.36 \text{ s}$). These data are very important as they serve as an independent validation of the method, where native, control animals and an elastase emphysema model were used.

Ruppert *et al.* used CSSR to observe the pulsatile flow of the capillary blood in healthy³³ and severe COPD³⁴ subjects. In healthy subjects the observed periodic signal reflects the pulsations of the blood throughout the cardiac cycle. Since these measurements are global, in order to measure this pulsation, the pulmonary blood flow had to be sufficiently in phase, so that the effects of temporal fluctuations are not averaged out. In COPD subjects, by contrast, the periodicity of the signal was largely lost. This might be due to the emphysematous lung tissue destruction or regional pulmonary hypertension, which could reduce the coherence of the pulsations.

They also used CSSR to measure septal tissue thickness h in 8 healthy non-smokers, 3 subjects with asthma, 1 subject with heavy second hand smoke exposure, and 3 smokers with COPD (1 with GOLD stage 0, and two with stage 3).³⁵ They observed higher h values in subjects with disease or with heavy smoke exposure compared to the healthy subjects. Very recently they reported another data set,³⁶ where they calculated RBC/TP ratio for 13 healthy non-smokers, 10 asthmatics and 10 COPD patients (4 with GOLD Stage 1, 3 with each stage 2 and 3). They defined the normal range for healthy subjects: $0.24 < \text{RBC/TP} < 0.33$, with 0.29 ± 0.04 (all but 1 lie within the range). For all diseased subjects the values of RBC/TP fell outside this range: in asthmatics RBC/TP values were split above (0.4 ± 0.04) and below (0.18 ± 0.03) the values observed in healthy volunteers, while for all COPD patients the values were below (0.15 ± 0.05) those seen in healthy subjects. The data is shown in Figure 19.6. All differences were statistically significant.

As mentioned in the introduction, it has been well-established morphometrically that S/V systematically decreases with increasing lung volume. However the details of the functional dependence between S and V remain obscure. It stands to reason that CSSR is uniquely poised to examine such a question in live awake humans. We used it to simultaneously measure F for a constant diffusion time while changing the lung volume.¹⁶ In this set of experiments the subjects were asked to inhale HPXe gas and air to TLC, and as soon as the CSSR pulse sequence started, the subjects would slowly exhale to Residual Volume RV ($\sim 8 \text{ s}$ exhalation). A MR safe spirometer, triggered by the spectrometer, was used to measure the exhaled volume while NMR data were collected. We measured F vs. LV for two diffusion times, 20 and 323 ms; the data and the fits are shown in Figure 19.7. Power-law fits of the data to $F = F_0 + CV^\alpha$ yielded the following for $t = 20 \text{ ms}$: $\alpha = -1.859$, $R^2 = 0.99$; and for $t = 323 \text{ ms}$: $\alpha = -1.856$,

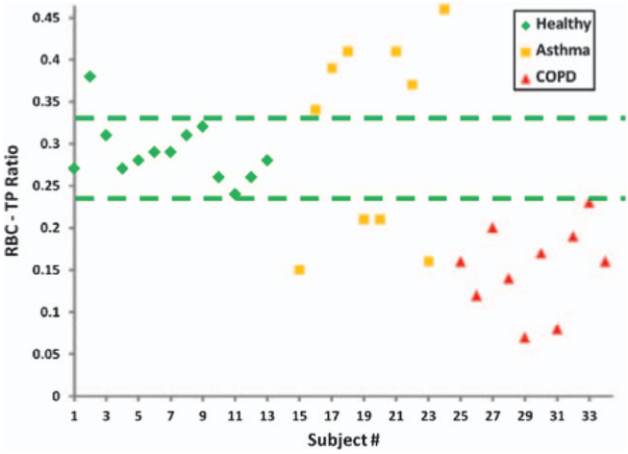


Figure 19.6 Averaged RBC-to-TP ratio for healthy (green), asthmatic (orange) and COPD (red) subjects at TLC.³⁶ The dashed lines mark the “normal” RBC-TP ratio that encompasses 92% of the healthy subjects but does not contain a single subject with lung disease.

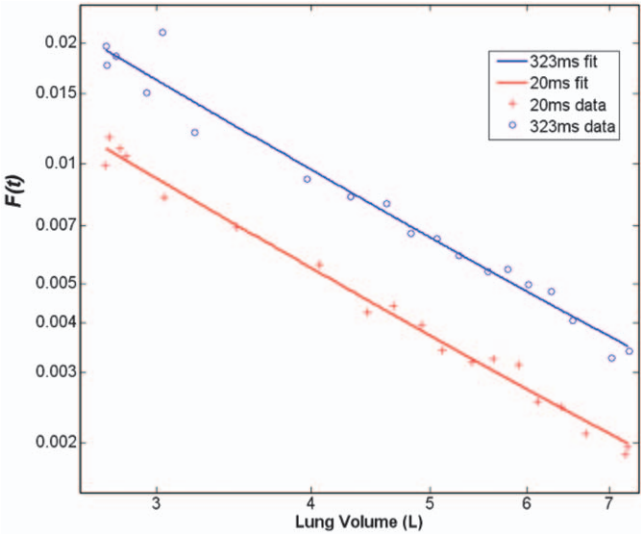


Figure 19.7 Examples of $F(t)$ versus lung volume acquired at a fixed diffusion time.¹⁶ Data are from a healthy, male subject, 32 years old, who exhaled from TLC to close to RV. Two different diffusion times (20 and 323 ms) were measured.

$R^2 = 0.97$. Due to the offset F_0 , it is not possible to convert these measurements into S/V , which requires several time points to evaluate the slope of F versus $\sqrt{t}$. Nevertheless, F is dominated by S/V .

19.4 Imaging of the Dissolved State

19.4.1 Direct Measurements

Regional maps of parameters reflecting lung function could provide new methods that are (a) more sensitive to changes in pathology than the existing methods and (b) have greater specificity in identifying the cause of any change in function. Due to the low tissue density in the lung and low solubility of xenon in the septum, less than 2% of the gaseous xenon diffuses into the septal wall, making a direct imaging of the dissolved state rather challenging.

Muradyan *et al.* used the 3-point Dixon technique^{37,38} to simultaneously image gas and dissolved states for the 1st time in humans, demonstrating the feasibility of such measurements. A simple gradient echo sequence was used for the data acquisition with three different echo times in order to properly separate gas and dissolved state signals and correct for field inhomogeneity. Two healthy subjects were imaged at $\sim 40\%$ (twice each) and $\sim 70\%$ of TLC. Since these were imaging sequences, only a single diffusion time was used. It was chosen based on the xenon uptake curves previously obtained on each of the subjects at the respective lung volumes, such that the semi-infinite slab model¹⁵ remained applicable. The measured values of the fractional gas diffusivity F had a higher mean value and heterogeneity for 40% TLC compared to the corresponding values at 70% TLC for both subjects (Figure 19.8). Although the SNR of the measurements was limited (average SNR for gas and dissolved state images were 20.5, 10.9 and 17.4, 6.5 for 40% and 70% TLC, respectively), it was possible to demonstrate the distribution of $F(t)$ through a direct measurement analogous to CSSR at two lung volumes, and observe the differences in the mean value and heterogeneity of F . However, for practicality, the SNR has to be addressed by improving the polarization, using more sophisticated sequences, or moving to higher field strength for optimized HPXe imaging (these measurements were performed at 0.2 T, and although in the case of hyperpolarized medium MRI the produced magnetization does not depend on the magnetic field strength, the overall SNR could be improved by using somewhat higher fields for optimal use of RF technology).

The 1st attempt to image xenon in tissue and plasma (TP) separately from xenon in RBC was made by Driehuys *et al.* in 2006 in rats, using an approach they called Xenon Alveolar Capillary Transfer imaging, XACT.¹³ In this study they, too, used the Dixon technique (to separate tissue-plasma signal from the RBC signal) with radial data acquisition to minimize the echo time. They employed an animal ventilator capable of delivering constant volume of gas to the animal thus enabling data averaging. Although the SNR's of the images of gas transfer to tissue-plasma and to RBC were low (~ 7), they were able to demonstrate severely impaired transfer of HPXe to RBC in a rat pulmonary fibrosis model. One of the observations was that in control animals there was a strong correlation between the number of pixels with

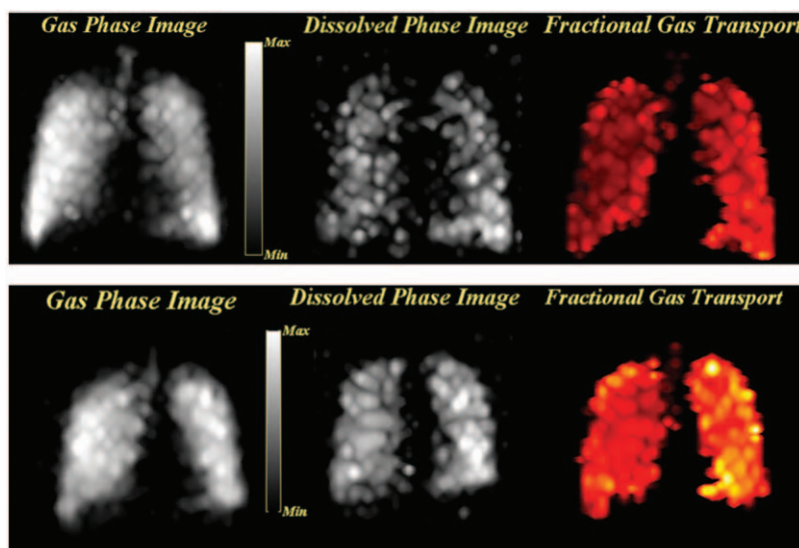


Figure 19.8 Gas and dissolved state images from a healthy subject at two different lung volumes, obtained using 3-point Dixon technique.^{37,38} The top row shows the data at higher lung volume ($\sim 70\%$ TLC), while the bottom one is at $\sim$ FRC. As expected, the higher lung volume shows more homogeneous distribution of the gas exchange. Also, $F(t)$ values at higher LV are lower than those at lower LV.

gas signal and both the number of pixels containing a TP signal and the number of pixels with a RBC signal. On the other hand, in the rats with fibrosis, while the correlation was similarly strong between gas pixel numbers and TP pixel numbers, it was significantly lower for the number of pixels with the RBC signal. They demonstrated a correlation between the regions of TP and RBC mismatch (where TP signal is present, while RBC signal is not replenished) and the histology, which showed these regions had tissue thickening. They calculated the mean ratio of saturation RBC to TP signals for both animal groups: there was a significant drop in the injured group ($\text{RBC/TP} = 0.59 \pm 0.24$) compared to the control group ($\text{RBC/TP} = 0.95 \pm 0.1$). It is worth mentioning that the values obtained from the images strongly agreed with the numbers obtained from spectroscopic measurements in the same rats.

In 2009, Driehuys *et al.*³⁹ demonstrated another, drastically different and potentially very promising approach to observe pulmonary function – they measured the gas phase xenon signal after an intravenous injection of HPXe dissolved into saline. The observed signal is proportional not only to perfusion, which is responsible for bringing the dissolved phase xenon into the lung, but also to the efficiency of gas exchange and the alveolar volume. Five seconds post injection of 5 mL xenon rich solution, they performed imaging using GRE, and obtained maps with $\text{SNR} = 25$.

Cleveland *et al.*⁴⁰ extended the direct imaging of the dissolved state in humans to 3D and demonstrated the feasibility of generating 3D images during a single, 16 second breath-hold. They optimized the parameters of a radial 3D pulse sequence and obtained dissolved state images with SNR's between 6 and 11. They obtained sets of images in prone (1 healthy volunteer) and supine (14 healthy volunteers) positions demonstrating directional heterogeneity consistent with the gravitational effects on ventilation and perfusion. Although this is a very significant step towards functional imaging of the lung, one would ideally collect ventilation and "perfusion" (dissolved state data) images simultaneously, as it has been shown extensively that the fractional diffusivity F changes with the lung volume and hence meaningful, quantitative conclusions can be drawn only when ventilation and perfusion information are obtained simultaneously.

This exact issue has been recently addressed by Mugler *et al.*⁴¹ They developed a method to simultaneously observe 3D distributions of ventilation and gas exchange. They used a gradient echo sequence with a properly chosen acquisition bandwidth, so that gas and dissolved state signals are fully separated into two images. They studied 6 healthy volunteers, 3 subjects with asthma and 2 subjects with COPD. All 5 subjects with lung disease showed more heterogeneous ventilation and xenon uptake distributions compared to those in healthy volunteers. Furthermore, they calculated the ratio of the dissolved state signal to the gas state signal (D/G) for each slice in a subset of subjects with identical imaging parameters. They observed that in contrast to the healthy subject, whose data showed significantly higher D/G in the dependent slices of the lungs, in the subject with COPD the direction was reversed: the dependent slices had lower values of the ratio. In the case of the subject with asthma, the direction of the D/G increase was similar to the healthy subject's case, however the amount of change was significantly reduced.

Kaushik *et al.*⁴² improved on the work by Cleveland *et al.*⁴⁰ and obtained both gas and dissolved phase images within a single breath-hold. While Mugler *et al.*⁴¹ used GRE with cleverly adjusted parameters to obtain D and G images side by side, Kaushik *et al.* used an interleaved excitation of each phase to obtain the images. They used a radial center-out acquisition to reduce echo times aiming for higher SNR. Nine healthy volunteers were studied in supine and prone positions to obtain gas and dissolved state images. The ratio of these images (D/G) yielded the so called xenon transfer map (XT). In supine subjects G, D and XT maps all exhibited an anterior-posterior gradient with slopes of 1.92 ± 1.73 , 3.46 ± 1.91 , and $2 \pm 0.74\% \text{ cm}^{-1}$, respectively. When prone, the gradient direction was reversed, resulting in a posterior-anterior gradient with the respective slopes of 0.28 ± 2.23 (G), 2.18 ± 2.47 (D), and 1.94 ± 1.14 (XT)% cm^{-1} . They also quantified the heterogeneity of G, D and XT maps through the calculation of their coefficients of variation (CV). The D maps had significantly higher CV's than the G maps in both supine and prone cases. Further, XT maps were significantly more uniform than either D or G, again in both prone and

supine cases. They observed no appreciable differences in CVs of G, D, and XT maps between prone and supine positions.

Qing *et al.*⁴³ extended the approach by Kaushik *et al.* discussed above, in combination with a Dixon-type approach, to separate the TP signal from the RBC signal, while simultaneously collecting the gas signal as well. Four ratios of the signals corrected for flip angle differences were calculated: tissue-plasma to gas (TP/G), RBC to gas (RBC/G), total dissolved state to gas (D/G) and RBC to tissue-plasma (RBC/TP). D/G reflects the gas uptake efficiency for the diffusion time dictated by the pulse sequence parameters; TP/G is indicative of the alveolar tissue volume, although only a single time point measurement is not very instructive; RBC/G, similar to D_{LCO} , is related to gas transport from alveoli to blood; and changes in RBC/TP may reflect the changes in the relative compartment sizes.

They studied 10 subjects, 5 healthy volunteers, 3 COPD subjects and 2 subjects with asthma. In 3 of the subjects they performed repeat scans to evaluate reproducibility. They also observed higher values of all ratios in the gravitationally dependent regions of the lungs and elevated values in 3 of the 4 ratios (all but RBC/TP) in disease. Further, significantly higher heterogeneity was observed in diseased subjects compared to the healthy subjects in all maps and ratios. The mean values obtained from the images and maps were in excellent agreement with the values measured globally using FID's. Finally, the reproducibility of the mean value of the ratios on a slice-by-slice basis was demonstrated to be quite high and in agreement with the global averages. The lowest reproducibility was found in RBC/G ratios ($\sim 12\%$). For D/G, TP/G and RBC/TP the respective reproducibilities were reported as 7%, 9%, and 5% for slice-by-slice means and 6%, 5% and 5% for the global means.

At the 2014 annual meeting of the International Society of Magnetic Resonance in Medicine, Qing *et al.* showed new data obtained using this technique, extended to a larger subject population (both healthy and asthmatic),⁴⁴ and to pediatric cystic fibrosis (CF) population.⁴⁵ They observed relatively high RBC/TP, low TP/G, and normal ADC values in 7 of 10 asthmatics. The pediatric CF group showed more heterogeneous TP maps compared to the healthy group, while RBC/TP maps in the CF group exhibited a uniform distribution. The overall gas uptake to the RBCs (RBC/G) for the CF subjects was similar to or higher than the corresponding value for the healthy group.

Reis *et al.*⁴⁶ used Chemical Shift Imaging (CSI) to image G, TP and RBC distributions in 5 healthy, 1 2nd hand smoker and 2 CF subjects. In the 2nd hand smoker they observed slightly higher TP/G and significantly lower RBC/G ratios compared to healthy volunteers. In CF patients both ratios were significantly lower than in healthy subjects. Fernandes *et al.*⁴⁷ used the same CSI approach to image G, TP and RBC distributions in 5 healthy, 1 2nd hand smoker, 1 smoker and 1 smoker with COPD subjects. They observed increased values of TP/RBC in active and 2nd hand smokers compared to healthy subjects. Moreover, TP/RBC was strongly correlated with the

subjects' FEV1/FVC. Unfortunately, they did not report on TP/G and RBC/G, hence it is impossible to determine whether the elevated TP/RBC is due to inflammation and increase in tissue thickness, delayed pulmonary gas transfer to the RBC, or diminished pulmonary perfusion.

19.4.2 Indirect Measurements

In parallel with the development of direct dissolved state imaging techniques, an indirect approach to evaluate regional lung function, Xenon Polarization Transfer Contrast (XTC), was suggested by Ruppert *et al.*⁴⁸ In XTC, a fractional depolarization F_{XTC} is estimated from the measurement of the hyperpolarized gas magnetization in the lungs before and after multiple consecutive inversions of the dissolved state magnetization. XTC, as originally conceived by Ruppert *et al.*¹⁴ required two breath-holds to incorporate a control experiment. During the first breath-hold, two gas phase images are collected measuring the cumulative attenuation from sources unrelated to interphase diffusion of xenon: the RF pulses used in the images; T_1 decay (primarily from oxygen in the lungs) during image acquisition; the effect of the inversion pulses applied off resonance (-205 ppm) on the gas phase magnetization, and T_1 relaxation during the application of N off-resonance inversion pulses. During the second breath-hold, again two images are collected separated by XTC generating pulses: during the time allowed for diffusion some of the gaseous xenon dissolves into tissue and blood. This magnetization is then inverted by the pulse applied at $+205$ ppm. Each pulse of the XTC sequence allows further interphase diffusion and depolarization of the gas phase magnetization. Repeated multiple times, this process attenuates the gas signal in the second image due to the diffusive gas transport F in addition to the other sources also present in the first breath-hold. Essentially by dividing the two measurements the attenuation caused by F is separated.

The next part of this chapter will cover further aspects and measurements of the XTC approach in more detail. This short review is to serve as an outline of other possibilities, either equivalent or complementary to the direct measurements of the dissolved state xenon *in vivo*.

Ruppert *et al.*¹⁴ demonstrated the feasibility of the technique on animals and argued that for diffusion times chosen to be sufficiently long to saturate the dissolved state, the depolarization map reflects only the local tissue volume, and not S/V . They showed that fractional depolarization increased with the decrease of the lung volume, and has higher values in the dependent regions of the lung compared to the independent regions. In a follow-up work Ruppert *et al.*⁴⁹ improved the sensitivity of the technique by optimizing the pulse sequence parameters, reducing the noise in the depolarization measurement to $\sim 3\%$, and estimating that the optimized XTC would be sensitive to tissue thickness changes as small as 300 nm.

Our group implemented XTC for human *in vivo* measurements.⁵⁰ We modified the technique to perform both the XTC and Control measurements

during a single breath-hold, thus alleviating the need for an error prone image registration procedure that would be required if the XTC and Control measurements were acquired in separate breath-holds. We called the modified technique Single Breath XTC (SB-XTC). Again, higher values of F in the gravitationally dependent lung¹⁹ were observed. We studied the fractional depolarization F as a function of lung volume in 8 healthy subjects⁵⁰ for a wide range of lung volumes, from 18% to 82% of TLC. We observed an increase in the value of $\langle F \rangle$ with the decrease of the lung volume (Figure 19.9A). We separated the physiological heterogeneity of the lung from the overall measured heterogeneity and observed a reduction of physiological heterogeneity with the lung volume decrease (Figure 19.9B).

Using SB-XTC we studied 2 non-smokers, 9 smokers (with a smoking history ranging between 1.5 and 33 pack years (PY)) and 3 non-smokers, who have seen heavy 2nd hand exposure to smoke (~ 13 –22 years of more than 10 h of daily exposure).⁵¹ We measured their average fractional gas transport $\langle F \rangle$ as a function of smoking history or exposure. The data is shown in Figure 19.10. As can be appreciated from the figure, in almost all smokers (except the smoker with the longest smoking history, 33 PY) we observed

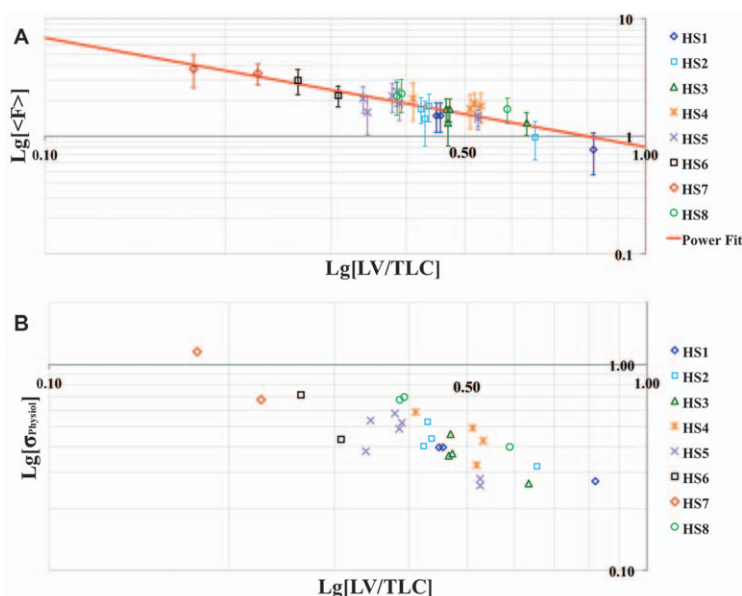


Figure 19.9 Volume dependence of the mean fractional gas transport $\langle F(t) \rangle$ (A) and physiological heterogeneity σ_{Physiol} (B) for eight healthy subjects (HS1-8), both plotted on a Log-Log scale.⁵⁰ To enable inter-subject comparison, the lung volumes are normalized to TLC of each subject. $\langle F(t) \rangle$ from all subjects is in good agreement within the error, which is represented here by the contribution of the noise to the width of the fractional gas transport distribution. In most cases the largest contribution to the width of $\langle F(t) \rangle$ distribution comes from the physiological heterogeneity.

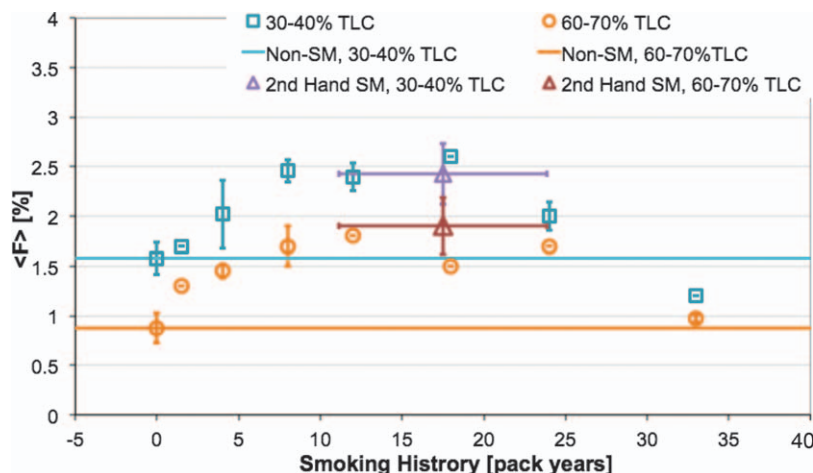


Figure 19.10 Mean Fractional transport $\langle F \rangle$ vs. smoking history at two lung volumes.^{38,51} Purple and red data points (triangles) are from 3 2nd hand smokers. Interestingly, the effect of 2nd hand smoke is similar to that of active smoking.

elevated $\langle F \rangle$ at both low and high lung volumes. Similarly high values of $\langle F \rangle$ were observed in 2nd hand smokers. This is suggestive of ongoing inflammation in the lungs. The lower value of $\langle F \rangle$ in the subject with 33 PY smoking history might be due to the interplay between inflammation, that results in an increase of the measured septal thickness, and lung tissue/capillary bed destruction, which lowers $\langle F \rangle$. Interestingly, the subjects with 2nd hand exposure exhibited an increase in $\langle F \rangle$ almost identical to that seen in active smokers.

We further extended the technique to 3D *in vivo* measurements for three diffusion times (20, 44, 66 ms) short enough to maintain the validity of the semi-infinite slab model.¹⁵ We used the short-time model to fit the data and obtain regional S/V in healthy subjects (Figure 19.11). Importantly, we demonstrated, that for the proper estimation of the fractional depolarization, it is necessary to account for non-uniform B_1 distribution. As mentioned earlier, f_D and F are only equivalent when 90° pulses are used for XTC. Therefore, 90° pulses must be used to utilize the analytical CSSR framework to calculate morphological parameters of the lung such as S/V , h , τ , etc.

Dregely *et al.*^{52,53} extended the SB-XTC approach even further, collecting 4 3D images during a single breath-hold, thus implementing a protocol that includes a Control experiment, and 2 XTC experiments with different diffusion times. They called this version of XTC Multiple exchange time XTC (MXTC). They studied 3 healthy volunteers, 1 subject with asthma and 2 subjects with COPD and measured the ratio of the parenchymal tissue, the alveolar gas volumes MXTC-F and a parameter MXTC-S, related to the wall thickness. It was shown that MXTC-S is elevated in lung disease, while MXTC-F might be sensitive to loss of functional tissue in a COPD subject.

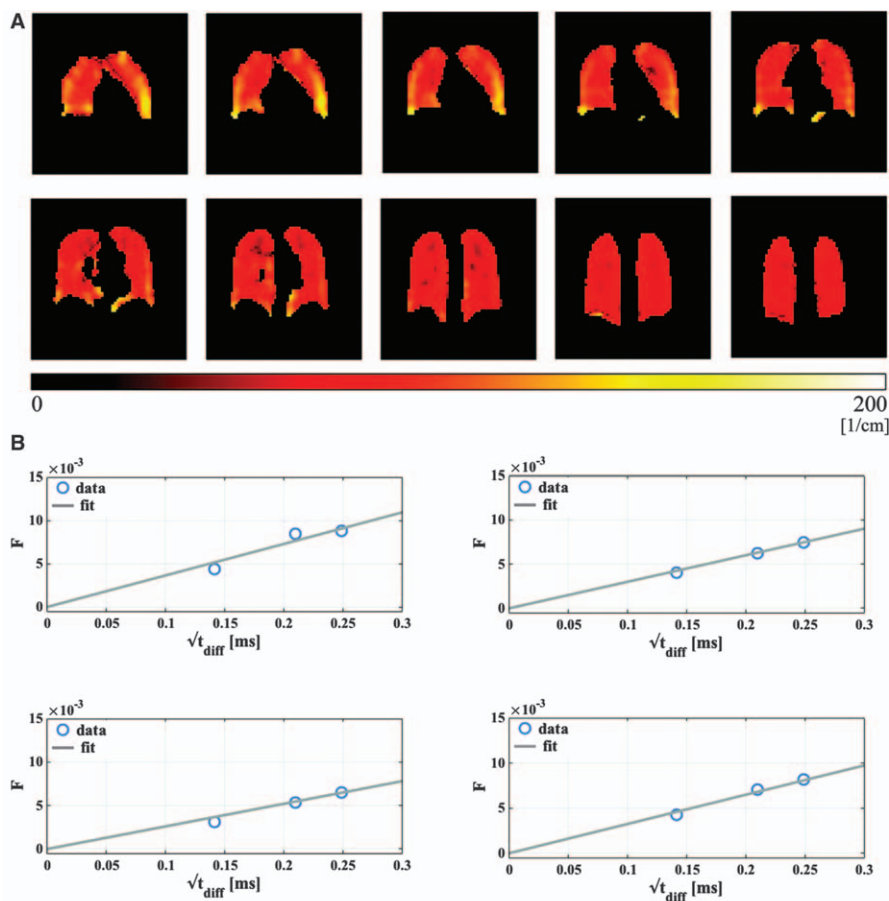


Figure 19.11 SB-XTC data from a healthy volunteer.⁵⁰ A – The S/V-maps of 10 slices (in the anterior-posterior order) in units of inverse cm, calculated from a pixelwise fit to the semi-infinite slab model. The global mean value for S/V is $89 \pm 30 \text{ cm}^{-1}$ (mean $\pm$ standard deviation). B – Representative voxel-wise fits of F to the semi-infinite slab model from four different voxels measured using three diffusion times – 20, 44 and 62 ms.

In one of the COPD subjects they saw a strong correlation of MXTC-F with CT. A significant gradient in MXTC parameters was observed at low lung volumes, consistent with gravity-induced lung tissue deformation in the supine imaging position. At high lung volumes the values for both, MXTC-F and -S were lower and the gradients less pronounced. This extension of the technique to include more diffusion time measurements in order to also obtain the local septal thickness is an important improvement. However, in such measurements one needs to be careful with the choice of imaging protocols and parameters. As we have demonstrated,⁵⁰ if no explicit B_1

distribution correction is implemented the values of the obtained parameters could be miscalculated. Further, since there is only a single control experiment for multiple diffusion times, one needs to ensure that the total time for XTC creation for both time points is the same, so that the T_1 effect for both XTC parts is identical and thus corrected for. And finally, since for different diffusion times the number of XTC RF pulses could be different, while the control part would match only one of these numbers, one has to ensure that the RF pulse applied at ± 200 ppm does not have any effect on the gas phase magnetization.

19.5 Discussion

A few things are worth mentioning. Firstly, it is beyond doubt that dissolved state xenon imaging is sensitive to lung function, and thus relevant to clinical use.

Secondly, a consensus on how these measurements should be done, what parameters should be obtained *etc.*, is yet to be reached. Although this is understandable, since we as a community are still in the process of developing the approaches, nevertheless it would be very helpful if the data would allow for a direct quantitative comparison of different approaches, which would in turn accelerate the progress and the acceptance of the methodology. The 1st steps in these directions have been taken by Stewart *et al.*,³⁰ who analyzed the same data set using different analytical models available for xenon uptake, and compared their results.

And thirdly, it has become clear that several diseases have been studied in some detail by a number of groups, allowing one to compare their findings.

For example, ILD, including IPF, seems to be studied the most, and it is clear that the total dissolved signal is significantly increased in subjects with fibrosis. Moreover, in several studies dramatic reductions in RBC signal and RBC/TP ratio are observed, while TP signal is increased. This is strongly suggestive of a thickening of the pulmonary tissue and a delayed delivery of xenon to the blood (or RBC).

It became evident that in the implementation of imaging techniques all researchers looked at the gravitationally dependent distribution of gaseous and dissolved state signals. The evidence of an anterior–posterior gradient in the supine position, and its reversal when prone has been reported.

Further, there are several studies looking at COPD patients (although still in small numbers). All groups report more heterogeneous distributions of TP, RBC and G signals in patients compared to healthy subjects; a reversal of the anterior–posterior gradient was noted, along with a less prominent slope. Lower values of D/G, RBC/G and RBC/TP were reported in patients compared to healthy subjects. In emphysema models of mice V_D/V_G was significantly lower, and strongly correlated with histology.

In asthma, again, heterogeneous distributions of TP, RBC, and G were observed, generally with lower values of TP and RBC signals compared to

healthy subjects. However, it seems that there is not yet a clear picture of the behavior of RBC/G, RBC/TP; they can be either higher or lower compared to healthy subjects.

There are a couple of studies looking at asymptomatic active and 2nd hand smokers. They report higher D/G ratios in both active and 2nd hand smokers, higher TP/RBC, suggesting a presence of inflammation. Also, a strong correlation of TP/RBC with FEV1/FVC has been reported.

There is a growing number of studies validating HPXe measurements against accepted standards. Some initial work has already been done. Butler *et al.*¹⁵ validated original *S/V* measurements in a porex phantom against optical microscopy; Driehuys *et al.*¹³ validated the xenon uptake measurements in a rat fibrosis model against histology, and reported strong correlation; Imai *et al.*³¹ validated V_D/V_G measurements with CSSR in an emphysema model against V_D/V_G obtained from histology, and observed a very strong correlation between the two; they also saw a strong correlation between V_D/V_G and L_m ; Kaushik *et al.*²⁹ and Liljeroth *et al.*²⁸ saw a correlation between RBC/TP and D_{LCO} in pulmonary fibrosis patients; Stewart *et al.*³⁰ reported on a correlation between the capillary transit time (measured with CSSR) and the whole lung pulmonary transit time obtained using DCE-MRI; Fernandes *et al.*⁴⁷ observed a correlation of TP/RBC with FEV1/FVC in 2nd hand smokers; Dregely *et al.*⁵³ showed a strong correlation between MXT-CF and lung density measure with CT.

To conclude, this field is in rapid development. Probing the dissolved state of HPXe is clearly of great interest as it has the potential to provide a wealth of diagnostically important information. Of course the low lung tissue density and the small partition coefficient render the task quite challenging. Most of the progress to date has been on the spectroscopic front. Nevertheless, very promising initial steps have been taken in the direction of dissolved state imaging. We are filled with enthusiasm for future developments in this exciting burgeoning field.

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¹²⁹Xe Chemical Shift and Spin–Lattice Relaxation Dependences on Blood Oxygenation

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20.1 Introduction

Changes in tissue oxygenation may provide an insight into extent of disease; for example, in the discrimination of the penumbra following stroke¹ or identification of ischemia following myocardial infarction.² Furthermore, hypoxia limits the efficacy of radiotherapy in the treatment of tumours.³ In asthma and COPD, hypoxia can influence the lifetime and the functionality of neutrophils that are associated with inflammation in the lungs.⁴ The accepted gold standard method of determining deep tissue oxygenation is by polarographic electrodes, as pioneered in the late 1950s.⁵ This invasive method, however, samples only a small amount of tissue and is able to provide assessment of oxygenation for only limited tissue volumes. Owing to this limitation, oxygenation is usually estimated using surrogate techniques,

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

such as the monitoring of mixed venous oxygenation, heart rate, blood pressure and oxygen saturation at the jugular bulb. However, these estimates can prove inaccurate as distal tissue oxygenation is not necessarily well represented by the more proximal measurements, or *vice versa*.⁶

Perfusion imaging can be used to measure blood delivery to a tissue, however oxygen supply and demand can be independent of one another, *e.g.* revascularisation of fibrotic tissue provides blood flow out of proportion to metabolic demand. Likewise, tissues with low levels of perfusion have an adequate oxygen supply while at rest, but an inadequate oxygen supply during periods of increased metabolic demand. Perfusion alone does not completely describe underlying physiology⁷ and thus direct, non-invasive measurement of blood oxygenation may be of interest in many clinical settings as well as being of good physiological interest.

As the treatment planning of many diseases depends on tissue oxygenation (*e.g.* radiotherapy response in hypoxic tumours⁸), several attempts have been made to quantify regional oxygenation using MRI. A promising method is the use of blood oxygen level dependent MRI,⁹ where oxygen and carbogen levels are cycled to generate images that indicate impaired oxygen uptake.¹⁰ However, this technique provides only qualitative estimates of tissue oxygen partial pressure¹¹ since there are endogenous variations in magnetisation relaxation parameters that can confound these measurements and make absolute oxygenation concentration determination difficult. Techniques that introduce exogenous tracers for MR oximetry, such as Overhauser enhanced MRI of unpaired radicals^{12,13} and ¹⁹F MRI,¹⁴ are promising for measurement of blood oxygenation, however they have yet to demonstrate uptake in humans. In the lungs, the T_1 of inhaled hyperpolarised ³He¹⁵ can be used to quantify regional alveolar oxygen concentration, but ventilation–perfusion mismatch means this does not necessarily reflect the capillary blood oxygenation.

Xenon has been in routine clinical use for many years as a tracer of blood perfusion¹⁶ and the physiological effects of xenon gas administration are well known and characterised.^{17,18} The nuclear polarisation of ¹²⁹Xe can be increased by 5–6 orders of magnitude by using the technique of spin-exchange optical pumping (SEOP).¹⁹ This “hyperpolarisation” enables the detection of ¹²⁹Xe with nuclear magnetic resonance (NMR) even at very small ¹²⁹Xe concentrations and, owing to its large, loosely bound electron cloud, ¹²⁹Xe NMR is highly sensitive to the xenon chemical environment, exhibiting a marked change in the resonance frequency when dissolved in different biological fluids and tissues.^{20,21}

Three distinct NMR peaks are observed *in vivo* when ¹²⁹Xe gas is inhaled into the lungs. The largest peak originates from ¹²⁹Xe gas in the air spaces and the two other peaks, centred approximately 200 ppm away from the gas peak, have been attributed to ¹²⁹Xe dissolved in alveolar tissue/blood plasma and in red blood cells (RBCs).^{22,23} Physiologically important information about gas exchange and uptake can be derived from the signal amplitudes and exchange kinetics of these discrete ¹²⁹Xe resonances.^{24,25}

This chapter provides a comprehensive evaluation of the exchange and relaxation dynamics of ¹²⁹Xe in whole blood. In particular, the relationship between blood oxygenation and the two ¹²⁹Xe NMR parameters, chemical shift and spin–lattice relaxation, are discussed with regards to previous and most recent findings.

20.2 Xenon–Hb Binding and the Magnetic Properties of Hb

In this section, the magnetic properties of haemoglobin (Hb) will be introduced along with current knowledge of the xenon binding sites in Hb.

20.2.1 Magnetic Properties of Haemoglobin

As first demonstrated by Pauling and Coryell,²⁶ the fully deoxygenated form of haemoglobin – deoxyhaemoglobin, Hb₄ (electron spin $S=2$) – is paramagnetic, whilst the fully oxygenated form – oxyhaemoglobin, Hb₄O₈ ($S=0$) – and carboxyhaemoglobin (Hb with carbon monoxide bound to it) are both diamagnetic. In addition, it was shown by Coryell *et al.*²⁷ that blood oxygen saturation (sO_2) measurement is essentially an ensemble average measure of the superposition of the two extreme haemoglobin states, Hb₄ and Hb₄O₈, with only a very small contribution from the three intermediate haemoglobin states (Hb₄O₂, Hb₄O₄ and Hb₄O₆). Furthermore, Coryell *et al.* determined that the relative fractions of haemoglobin in the fully deoxygenated and fully oxygenated state vary approximately linearly with blood oxygenation – see Figure 20.1, (b).

20.2.2 Xenon–Hb Binding

Xenon has a large, polarisable electron cloud and, mainly through van der Waals interactions (London dispersion forces), xenon atoms are able to form transient bonds with a number of macromolecules which contain hydrophobic cavities.^{28–30} Although xenon has no relevant biological function, owing to its lipophilic nature, it is frequently used in X-ray crystallography as a probe to identify the locations of non-polar haemoglobin (Hb)/myoglobin (Mb) cavities which may be involved in gas ligand (*e.g.* CO, O₂ and NO) migration.^{31–34} The first X-ray crystallography experiments reporting xenon binding in blood were performed in the 1960s by Schoenborn *et al.*, who identified only one xenon binding site in both sperm whale Mb³⁵ (proximal to the iron haem) and horse Hb³⁶ (distal to the iron haem). Following from this, Tilton *et al.*³⁷ examined crystal structures of myoglobin pressurised under several atmospheres of xenon gas, revealing not only one, but four unique xenon–Mb binding sites.

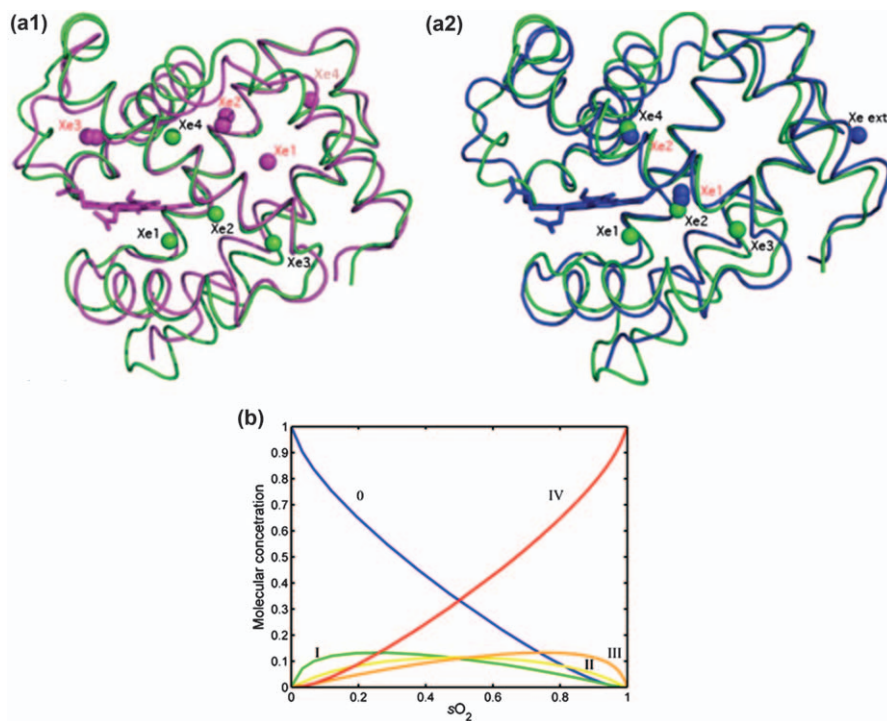


Figure 20.1 Xenon binding sites with Hb and Mb molecules. (a1) Hb α chains (purple) and (a2) Hb β chains (blue) superimposed to Mb (green). The haem groups are represented as sticks. The pink Xe4 in the α chain of Hb is located approximately at the xenon binding site identified by Schoenborn in horse Hb³⁶ distal (38 Å) to the haeme iron. The xenon site closest to the haem iron in the α chain of Hb is Xe3, which is proximal (~ 9 Å) to the haeme iron. Figure adapted from ref. 39 with permission. Copyright 2009 by John Wiley and Sons. (b) Concentrations of molecular Hb species as functions blood oxygenation. 0 = Hb₄; I = Hb₄O₂; II = Hb₄O₄; III = Hb₄O₆; IV = Hb₄O₈ in horse haemoglobin. Data extrapolated from ref. 27 with permission. Copyright 1939 by American Chemical Society.

Xenon has most recently been used to examine CO and O₂ binding within human haemoglobins,^{34,38} and Savino *et al.*,³⁹ who closely examined hydrophobic cavity patterns in human Hb, identified a total of twelve xenon docking sites per Hb tetramer: four xenon binding sites are located in the α_1 chain, three in the α_2 chain and two in each β chain. An extra xenon atom is located at the surface of the β_2 subunit, labelled as Xe ext in Figure 20.1, (a2). It was shown, from the topological differences in the xenon cavity sites (Figure 20.1, (a1) and (a2)), that there is no correspondence between xenon occupation in Mb and in Hb α chains. The xenon binding sites in oxygenated haemoglobin were not considered in this study. The Hb molecule undergoes a significant structural change as it makes the transition from the

deoxyhaemoglobin conformation to the oxyhaemoglobin conformation;⁴⁰ it is thus possible – and indeed likely – that the number/locations of xenon binding sites is/are different in deoxyhaemoglobin when compared to oxyhaemoglobin.

20.3 Two-site Exchange Model

20.3.1 Fractional Populations and Xenon Exchange Rates in RBCs and Plasma

For ¹²⁹Xe nuclei freely diffusing between RBCs and plasma within whole blood samples, a two-site exchange process is considered (Figure 20.2):



where k_a and k_b denote the exchange rates of ¹²⁹Xe diffusing from RBCs to plasma and *vice versa*. For dynamic equilibrium, the fractional populations of ¹²⁹Xe in RBCs and plasma, p_a and p_b , are related to the residency times τ_a ($\equiv k_a^{-1}$) and τ_b ($\equiv k_b^{-1}$) by

$$p_a = \frac{\tau_a}{\tau_a + \tau_b} \quad \text{and} \quad p_b = \frac{\tau_b}{\tau_a + \tau_b} \quad (20.2)$$

where $p_a + p_b = 1$ and the time taken, τ_{ex} , for the system to establish equilibrium is given by^{41,42}

$$\frac{1}{\tau_{\text{ex}}} = \frac{1}{\tau_a} + \frac{1}{\tau_b} = k_{\text{ex}} = k_a + k_b \quad (20.3)$$

where, k_{ex} is defined as the exchange rate constant. Combination of eqn (20.2) and (20.3) yields

$$\tau_{\text{ex}} = p_a \tau_b = p_b \tau_a \quad (20.4)$$

The ratio of residency times of ¹²⁹Xe in the plasma and RBCs can be estimated by recasting eqn (20.4) with fractional magnetisations in place of fractional populations,

$$M_a \tau_b = M_b \tau_a \Rightarrow \frac{M_b}{M_a} = \frac{\tau_b}{\tau_a} \quad (20.5)$$

where M_a and M_b are the fractional ¹²⁹Xe magnetisations in RBCs and plasma. With knowledge of the residency time ratio and the equilibrium time constant, τ_{ex} , which has been calculated previously by Bifone *et al.*⁴³ to be 12 ms, eqn (20.3) can be rearranged so that the individual ¹²⁹Xe residency times in RBCs and plasma are

$$\tau_a = \left(\frac{\tau_a}{\tau_b} + 1 \right) \tau_{\text{ex}} \quad \text{and} \quad \tau_b = \left(\frac{\tau_b}{\tau_a} + 1 \right) \tau_{\text{ex}} \quad (20.6)$$

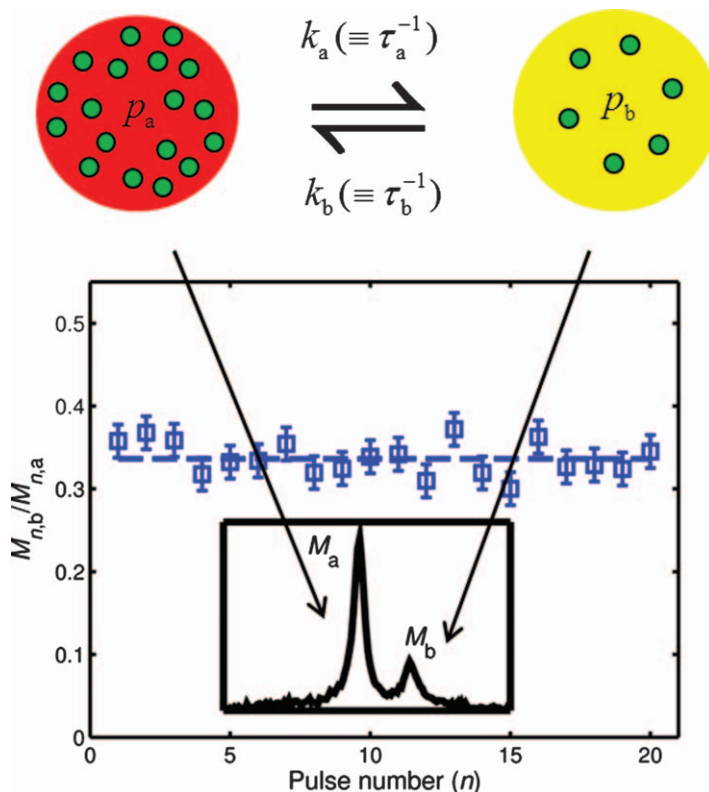


Figure 20.2 Two-site exchange model for xenon diffusing between red blood cells (RBCs) and plasma in whole blood. At dynamic equilibrium, the fractional populations of xenon within RBCs and plasma are denoted p_a and p_b , respectively, and the exchange rates are given by k_a and k_b . The inset shows a ^{129}Xe -blood spectrum at 1.5 T where the fractional ^{129}Xe -RBC and ^{129}Xe -plasma magnetisations, M_a and M_b (resonances separated by ~ 25 ppm), are equivalent to the fractional xenon populations.

Figure adapted from ref. 52 with permission. Copyright 2014 by John Wiley and Sons.

The magnetisation ratio, M_b/M_a , will depend on the haematocrit or red blood cell concentration (HCT) of the blood samples and the relative xenon solubilities in plasma and RBCs, so that the xenon residency times vary with HCT according to

$$\frac{M_b}{M_a} = \frac{\delta_b}{\delta_a} \left[\frac{1 - \text{HCT}}{\text{HCT}} \right] = \frac{\tau_b}{\tau_a} \Rightarrow \frac{\delta_b}{\delta_a} = \frac{\tau_b}{\tau_a} \left[\frac{\text{HCT}}{1 - \text{HCT}} \right] \quad (20.7)$$

where δ_b/δ_a is the plasma-RBC partition coefficient for xenon (δ_b and δ_a refer to the xenon solubility in plasma and RBCs, respectively).

20.3.2 ¹²⁹Xe Magnetisation Dynamics in Whole Blood

It is assumed that the ¹²⁹Xe resonance frequency at each site, ω_a and ω_b , is distinct, with a frequency difference given by $\Delta\omega = |\omega_a - \omega_b|$; the magnetisation dynamics of ¹²⁹Xe nuclei undergoing exchange between plasma and RBCs may then be described by coupled rate equations by extending previous NMR analysis of water protons diffusing between plasma and RBCs⁴⁴

$$\begin{aligned}\frac{dM_a(t)}{dt} &= -(R_{1,a} + k_a)M_a(t) + k_b M_b(t) \\ \frac{dM_b(t)}{dt} &= -(R_{1,b} + k_b)M_b(t) + k_a M_a(t)\end{aligned}\quad (20.8)$$

where $R_{1,a}(\equiv 1/T_{1,a})$ and $R_{1,b}(\equiv 1/T_{1,b})$ are the intrinsic NMR relaxation rates of dissolved ¹²⁹Xe nuclei in RBCs and plasma. Such systems have been considered in detail by Woessner⁴⁵ and the general solutions to eqn (20.8) are

$$\begin{aligned}M_a(t) &= A_+ \exp(-\phi_+ t) + A_- \exp(-\phi_- t) \\ M_b(t) &= B_+ \exp(-\phi_+ t) + B_- \exp(-\phi_- t)\end{aligned}\quad (20.9)$$

where

$$2\phi_{\pm} = (R_{1,a} + R_{1,b} + k_a + k_b) \pm [(R_{1,a} - R_{1,b} + k_a - k_b)^2 + 4k_a k_b]^{1/2} \quad (20.10)$$

and the coefficients A and B depend on the fractional volume of the RBCs and plasma (and the solubility of xenon in each compartment), as well as on $\phi_{\pm}$. The ¹²⁹Xe exchange rates, k_a and k_b , have been previously measured by Bifone *et al.*⁴³ in (slightly diluted) whole blood to be of the order of tens of Hz, whereas the ¹²⁹Xe relaxation times, $1/T_{1,a}$ and $1/T_{1,b}$, are in the sub Hz range, based on previous measurements by Wolber *et al.*⁴⁶ and Albert *et al.*⁴⁷ In the limit of $k_a, k_b \gg R_{1,a}, R_{1,b}$, eqn (20.10) can be approximated to

$$2\phi_{\pm} = (R_{1,a} + R_{1,b} + k_a + k_b) \pm k_a + k_b \quad (20.11)$$

so that the fast and slow decay rate constants, ϕ_+ and ϕ_- , are

$$\phi_+ = \frac{R_{1,a} + R_{1,b}}{2} + (k_a + k_b) \quad (20.12)$$

$$\phi_- = \frac{R_{1,a} + R_{1,b}}{2} \quad (20.13)$$

Considering the typical inter-pulse delay times used in ¹²⁹Xe-blood relaxation rate measurements (0.15–0.5 s),^{48,52} inserting the fast decay rate constant, ϕ_+ , into eqn (20.9) (due to the large value of $k_a + k_b$) causes

$A_+ \exp(-\phi_+ t)$ and $B_+ \exp(-\phi_+ t) \rightarrow 0$, so that the solutions to eqn (20.8) become

$$\begin{aligned} M_a(t) &= A_- \exp(-\phi_- t) \\ M_b(t) &= B_- \exp(-\phi_- t) \end{aligned} \quad (20.14)$$

suggesting that in the case of $k_a, k_b \gg R_{1,a}, R_{1,b}$, the ^{129}Xe magnetisations in both the plasma and RBC compartments decay with a common rate constant, ϕ_- , which we shall refer to as the observable ^{129}Xe relaxation rate, $R_1 (\equiv 1/T_1)$, in whole blood samples.

The ^{129}Xe relaxation rate, $1/T_{1,b}$, in the plasma pool is assumed to be dominated by dipole-dipole interactions with dissolved paramagnetic molecular oxygen, and should therefore change linearly with oxygen concentration, $[\text{O}_2]$, according to

$$\frac{1}{T_{1,b}} = r_{\text{O}_2} [\text{O}_2] + \frac{1}{T_{1,b}^0} \quad (20.15)$$

where r_{O_2} is the ^{129}Xe - O_2 relaxivity in plasma and $1/T_{1,b}^0$ is the ^{129}Xe relaxation rate in the absence of dissolved oxygen. The intrinsic ^{129}Xe relaxation rate for xenon dissolved in RBCs, $1/T_{1,a}$, can be obtained by combining eqn (20.13) (where $\phi_- = 1/T_1$, $R_{1,a} = 1/T_{1,a}$ and $R_{1,b} = 1/T_{1,b}$) and eqn (20.15), yielding

$$\frac{1}{T_{1,a}} = \frac{2}{T_1} - \frac{1}{T_{1,b}} = \frac{2T_{1,b}^0 - T_1(r_{\text{O}_2}[\text{O}_2]T_{1,b}^0 + 1)}{T_1 T_{1,b}^0} \quad (20.16)$$

20.4 *In vitro* Xenon–Blood Dissolution Techniques

In previous experiments with hyperpolarised ^{129}Xe in blood, saline was either presaturated with xenon and added to the blood samples,^{46,48} incurring associated dilution effects, or the xenon was slowly bubbled through small capillaries into the blood sample, opening up the possibility of unwanted gas bubble formation.⁴⁷

In our most recent ^{129}Xe blood experiments, to ensure effective mixing, the xenon and blood were passed through an exchange module^{49–51} (Superphobic MicroModule 0.5×1 G680 Contactor, Membrana, USA), which provided an exchange surface area of 100 cm². To perform the mixing, 10 mL of xenon gas was passed unidirectionally through the inside of thin-walled hollow-fiber tubes within the exchange module (Figure 20.3, (i)) at a rate of $\sim 1 \text{ mL s}^{-1}$, while the blood was passed back and forth over the outside of the tubes for $\sim 10 \text{ s}$ to ensure a sufficient concentration of xenon was dissolved into the blood. Using this mixing technique enables microscopic mixing, whilst also eliminating the formation of gas bubbles in the blood. Please see ref. 52 for full details on the experimental techniques for xenon–blood dissolution and blood oxygenation measurements.

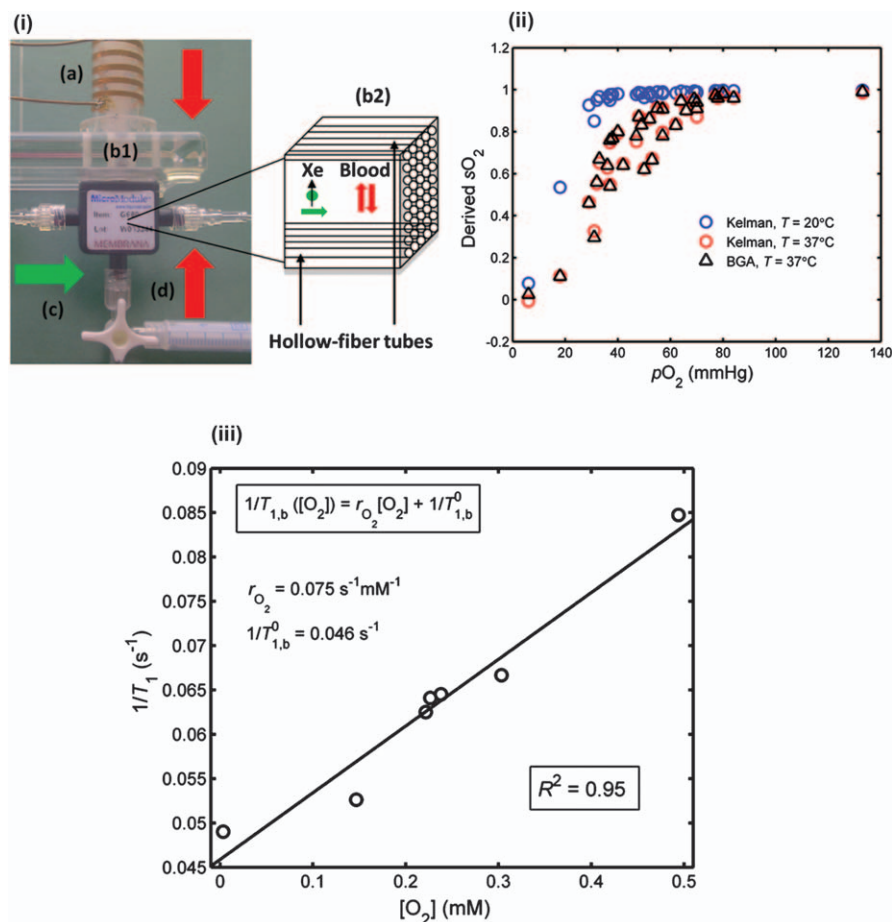


Figure 20.3 (i) (left) Photograph of xenon–blood exchange apparatus and (right) cross section of exchange module. Xenon, (c), is pushed through the hollow-fiber tubes of the exchange module, (b1) and (b2), unidirectionally at a rate of $\sim 1 \text{ mL s}^{-1}$, while the blood, (d), is passed into and out of the membrane and the sample volume (3 mL syringe enclosed within a custom-built solenoid RF coil, (a)). (ii) Derived blood oxygenation, $s\text{O}_2$, vs. measured blood oxygen partial pressure, $p\text{O}_2$. The blood oxygenation was derived numerically from blood $p\text{O}_2$, pH and $p\text{CO}_2$ values measured using a blood gas analyser. The blue and red circles correspond to oxygenation values derived using numerical methods based on Kelman⁷⁸ assuming blood sample temperatures of 20°C (sample temperature at which the NMR was performed) and 37°C , respectively, and the black triangles correspond to oxygenation values derived by the blood gas analyser (which assumes a sample temperature of 37°C). (iii) ^{129}Xe relaxation rates from NMR experiments performed on isolated plasma samples for a range of oxygen concentrations, $[\text{O}_2]$. A linear fit (with a coefficient of determination $R^2 = 0.95$) was performed on the data using the boxed equation, allowing determination of the ^{129}Xe – O_2 relaxivity in plasma, $r_{\text{O}_2} = 0.075 \text{ s}^{-1} \text{ mM}^{-1}$ and the ^{129}Xe relaxation rate in the absence of dissolved molecular oxygen, $1/T_{1,b}^0 = 0.046 \text{ s}^{-1}$. (i), (ii) and (iii) taken from ref. 52 with permission. Copyright 2014 by John Wiley and Sons.

20.5 ^{129}Xe Relaxation and Exchange in Human Blood

20.5.1 ^{129}Xe Relaxation Measurements in Whole Blood and Isolated Plasma

The ^{129}Xe relaxation rate in blood has been studied in previous NMR experiments performed by several groups. In work conducted at a field strength of 4.7 T with hyperpolarised ^{129}Xe , Albert *et al.*⁴⁷ found that the ^{129}Xe spin–lattice relaxation time, T_1 , in red blood cells (RBC) increased with blood oxygenation, measuring T_1 values of 4 s and 13 s in deoxygenated and oxygenated blood, respectively. The same group also performed measurements with thermally polarised ^{129}Xe samples and found the ^{129}Xe –RBC T_1 in deoxygenated and oxygenated blood samples to be lower with values of 2.7 ± 0.2 s and 7.88 ± 0.16 .⁵³ Wolber *et al.*,⁴⁶ at a field strength of 1.5 T, also reported an increase in ^{129}Xe T_1 with blood oxygenation (2.88 ± 0.27 s for deoxygenated and 5.71 ± 0.35 s for oxygenated blood), and found the T_1 ($1/T_1$) to increase (decrease) non-linearly with blood oxygenation.¹ In addition, both groups found the ^{129}Xe T_1 to be highest in blood that had been equilibrated with carbon monoxide; Albert *et al.*⁵³ reported a value of 11 ± 2 and Wolber *et al.*⁴⁶ reported a value of 7.84 ± 0.47 s.

In a study conducted by Tseng *et al.*,⁵⁴ with blood-foam at a field strength of 4.7 T, the opposite dependence of T_1 on blood oxygenation was observed when compared with ref. 47 and 46. The T_1 was reported to decrease from 40 s in deoxygenated blood to 20 s in oxygenated blood, and it was deduced that interactions between xenon and paramagnetic bubbles of oxygen gas in the blood was the principal cause of spin–lattice relaxation. The interior of the bubbles, within the blood-foam, provide a residency space for gaseous xenon and oxygen, and the bubble-wall provides a surface compartment for the oxygen-exposed gaseous xenon in which to dissolve. Xenon gas and paramagnetic oxygen gas in the bubbles (undergoing nuclear-electron dipole–dipole T_1 relaxation with a dependence inversely proportional to $p\text{O}_2$) can readily exchange with the dissolved xenon in this regime and the effect of oxygen on the ^{129}Xe T_1 may have been overestimated as such.

In our recent measurements, ^{129}Xe –RBC relaxation was examined over the widest yet range of blood oxygenations ($s\text{O}_2$ values of 0.06–1.00) using hyperpolarised ^{129}Xe ⁵⁵ at a field strength of 1.5 T. A quantitative analysis using the two-site exchange model outlined in Section 20.3.2 was done in order to determine parameters that underpin ^{129}Xe relaxation mechanisms in whole blood samples. Blood gas analysis parameters are shown in Table 20.1, alongside ^{129}Xe T_1 values corresponding to venous blood ($s\text{O}_2$ range 0.60–0.80), arterial blood ($s\text{O}_2$ range 0.95–1.00) and blood outside the physiological range ($s\text{O}_2 < 0.60$).[†]

[†]Note that all blood samples were obtained through venipuncture and we refer to blood as venous or arterial for $s\text{O}_2$ ranges of 0.60–0.80 and 0.95–1.00, respectively.

Table 20.1 ^{129}Xe relaxation times, T_1 , and rates, $1/T_1$, calculated from n samples for a variety of blood oxygenation, $s\text{O}_2$, values. The samples are as follows: arterial (defined here to be the range $s\text{O}_2 = 0.95\text{--}1.00$) blood from three volunteers (numbered A1–A3); a single venous blood sample, V2 (defined for $s\text{O}_2 = 0.60\text{--}0.80$); a blood sample equilibrated with carbon monoxide, CO; blood samples outside the physiological blood oxygenation ($s\text{O}_2 < 0.60$), D2; and samples of isolated plasma solution, P. The concentration of haemoglobin in the blood is denoted ctHb. $s\text{O}_2$ values were derived numerically from $p\text{O}_2$, $p\text{CO}_2$, and pH values that were measured on a blood gas analyser (see Figure 20.3, (i)).

Sample	T_1/s	$1/T_1/\text{s}^{-1}$	n	$s\text{O}_2$	$p\text{O}_2/\text{mmHg}$	$p\text{CO}_2/\text{mmHg}$	pH	ctHb/ mM
A1	3.4–7.8	0.29–0.13	11	0.96–1.00	33–133	27–74	7.13–7.5	9–12
A2	3.7–7.2	0.27–0.14	11	0.95–1.00	36–80	10–50	6.96–7.6	7.6–10.6
A3	3.6–6.1	0.28–0.16	4	0.97–0.99	47–84	23–48	7.14–7.4	8.1–8.7
V2	2.8	0.36	1	0.80	31	65	6.93	7.8
D2	2.2, 2.3	0.45, 0.43	2	0.06, 0.47	6, 18	89, 77	6.94, 6.92	7.4, 7.8
CO	7.9	0.13	2	—	—	—	—	—
P	11.4–20.4	0.09–0.05	7	—	2–303	7–96	6.8–7.5	—

^{129}Xe –blood NMR spectra obtained from all samples exhibited two distinct resonance peaks of 195 ppm and 220 ppm corresponding to xenon dissolved in blood plasma and RBCs, respectively, with reference to the ^{129}Xe gas peak at 0 ppm – see Figure 20.4 (a).

A T_1 measurement sequence was applied, consisting of 15–20 pulses with TR values of 150 ms and 500 ms for blood $s\text{O}_2$ ranges of 0.06–0.80 and 0.80–1.00, respectively. ^{129}Xe T_1 s were calculated by fitting the decay in the ^{129}Xe –RBC and ^{129}Xe –plasma NMR signals to the relationship,

$$S_n = S_0 \sin \alpha (\cos \alpha)^{n-1} \exp(-(n-1)TR/T_1) \quad (20.17)$$

where S_0 is the signal intensity at time $t = 0$, α is the flip angle and n is pulse number. The signals that were fitted to eqn (20.17), were determined by integrating over the ^{129}Xe –RBC and ^{129}Xe –plasma resonance peaks in the phased absorption spectrum (Figure 20.4, (a) for a zeroth-order phase-corrected absorption spectrum). See Figure 20.4, (b) for typical ^{129}Xe –blood decay spectra, with an inset showing fits to the ^{129}Xe –RBC and ^{129}Xe –plasma signal decays. The T_1 values calculated from the ^{129}Xe signal decay in RBCs were found to be the same (within experimental error) as the T_1 values calculated from the ^{129}Xe signal decay in plasma, thus confirming the prediction of eqn (20.14) (for $k_a, k_b \gg R_{1,a}, R_{1,b}$) that the ^{129}Xe magnetisations in plasma and RBCs in whole blood samples decay with a common observable T_1 . The overall ^{129}Xe –blood relaxation rate, $1/T_1$, was found to be non-linearly dependent on blood oxygenation, over an $s\text{O}_2$ range of 0.06–1.00, as shown in Figure (20.5, (c) and (d)). The non-linear relationship between $1/T_1$ and $s\text{O}_2$ can be fitted to the empirical equation

$$\frac{1}{T_1} = \kappa [1 - \exp(r_{s\text{O}_2} s\text{O}_2)] + \frac{1}{T_{1\text{dHb}}} \quad (20.18)$$

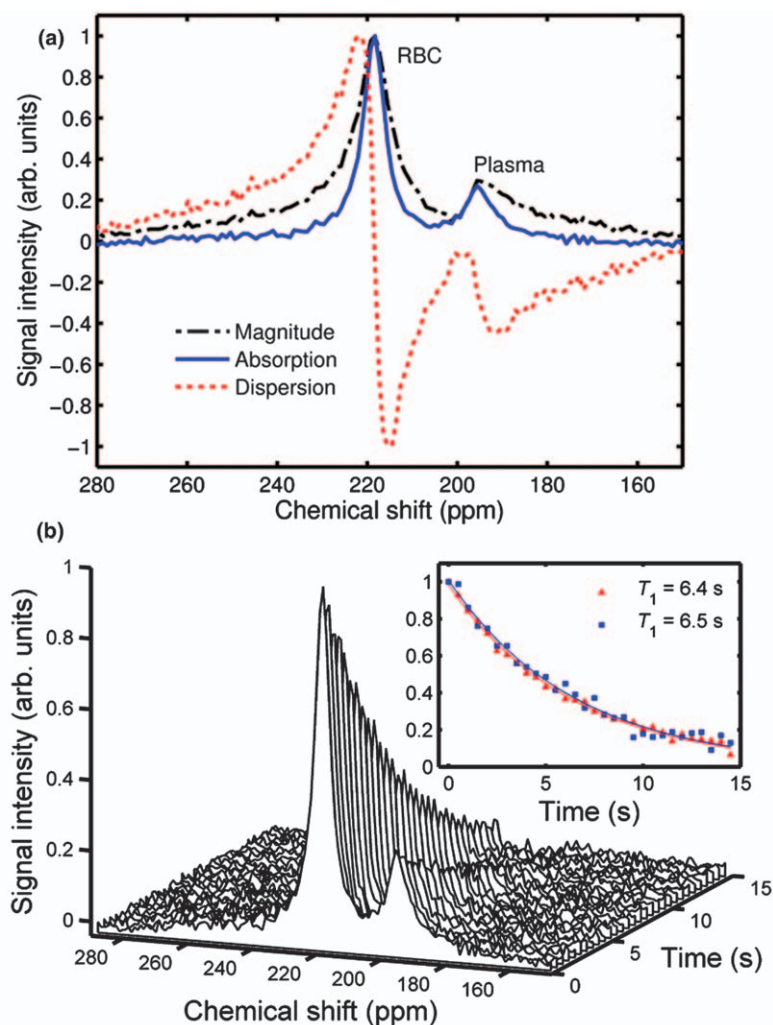


Figure 20.4 (a) ^{129}Xe NMR spectrum in blood at 1.5 T. The peaks at ~ 195 and 220 ppm correspond to ^{129}Xe dissolved within blood plasma and red blood cells, respectively. All data analyses were performed using the absorption part of the ^{129}Xe -blood signal, obtained by performing zeroth order phase corrections on the real and imaginary parts of the Fourier transformed spectra. (b) Decaying spectra from ^{129}Xe dissolved in blood acquired with 20 hard pulses of $500\ \mu\text{s}$ width (and inter-pulse delay = $0.5\ \text{s}$). The inset shows a fit performed on the decreasing ^{129}Xe NMR signal (integrals of ^{129}Xe -RBC and ^{129}Xe -plasma absorption peaks) in order to establish ^{129}Xe -RBC (red triangles) and ^{129}Xe -plasma T_1 values (blue squares). The decaying spectra represent a blood sample with $s\text{O}_2 = 0.98$. (a) and (b) taken from ref. 52 with permission. Copyright 2014 by John Wiley and Sons.

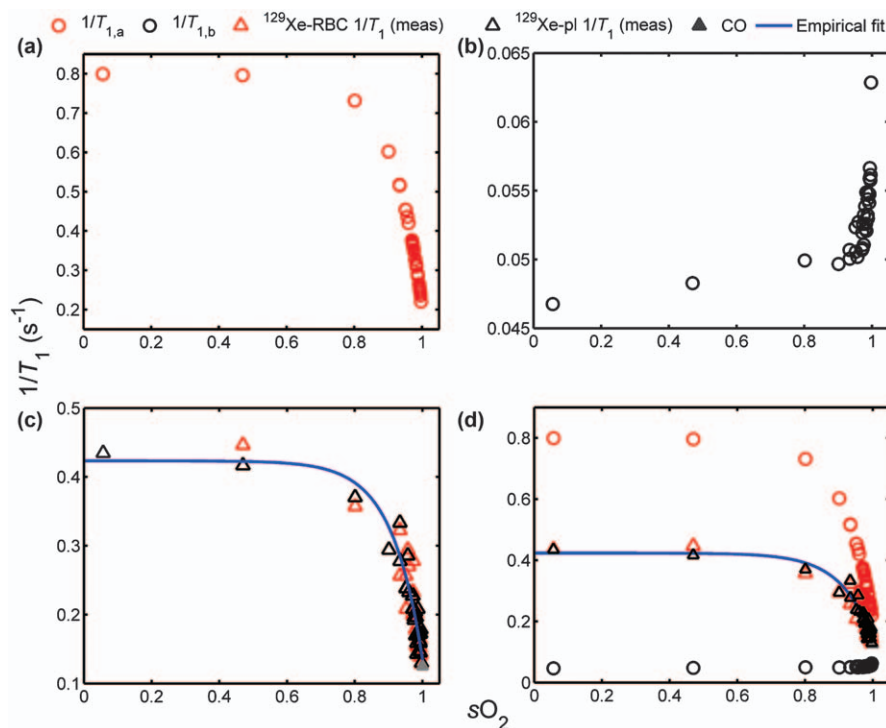


Figure 20.5 The ^{129}Xe relaxation rates from NMR experiments performed on six different blood samples taken from three separate volunteers covering the full blood oxygenation range. (a) and (b) show predicted intrinsic ^{129}Xe relaxation rates in RBCs, $1/T_{1,a}$, and plasma, $1/T_{1,b}$, respectively: $1/T_{1,a}$ was calculated using eqn (20.19), and $1/T_{1,b}$ was calculated from eqn (20.15). The data in (c) are the measured ^{129}Xe relaxation rates in RBCs (red triangles) and plasma (black triangles). An empirical function (eqn (20.18)) was fit to the data, where the following constants were determined: $\kappa = 4.6 \times 10^{-6} \text{ s}^{-1}$, $r_{s\text{O}_2} = 11.1$ and $1/T_1^{\text{dHb}} = 0.42 \text{ s}^{-1}$ ($T_1^{\text{dHb}} = 2.4 \text{ s}$). The solid gray triangle represents the ^{129}Xe relaxation rate for a blood sample that was equilibrated with carbon monoxide and (d) presents all data plotted together. (a)–(d) taken from ref. 52 with permission. Copyright 2014 by John Wiley and Sons.

where κ is a scaling constant, $r_{s\text{O}_2}$ we define here to be a relaxivity index characterising the rate of change of ^{129}Xe relaxation as a function of blood oxygenation and $1/T_1^{\text{dHb}}$ is the relaxation rate for fully deoxygenated blood ($s\text{O}_2 = 0.00$). The values of these constants, obtained by fitting eqn (20.18) to the ^{129}Xe relaxation rate values measured in plasma and RBCs – shown in Figure 20.5, (c) and (d) – were derived to be $\kappa = 4.6 \times 10^{-6} \text{ s}^{-1}$, $r_{s\text{O}_2} = 11.1$ and $1/T_1^{\text{dHb}} = 0.42 \text{ s}^{-1}$ ($T_1^{\text{dHb}} = 2.4 \text{ s}$). In addition, by setting $s\text{O}_2$ equal to 1.00 in eqn (20.18), one can obtain the relaxation rate of ^{129}Xe in fully oxygenated blood, $1/T_1^{\text{oHb}} = 0.13 \text{ s}^{-1}$ ($T_1^{\text{oHb}} = 7.7 \text{ s}$).

The measured values of ^{129}Xe T_1 range from 2.2 s in approximately fully deoxygenated blood ($s\text{O}_2 = 0.06$) to 7.8 s in fully oxygenated blood ($s\text{O}_2 = 1.00$). The rate of change of ^{129}Xe relaxation with respect to oxygenation is relatively slow in the $s\text{O}_2$ range 0.06–0.90, with the T_1 increasing from a value of 2.2 s to only 2.8 s; above $s\text{O}_2 = 0.90$, the rate of change of relaxation with blood oxygenation is much more rapid. The average range of ^{129}Xe T_1 in arterial blood samples from three separate volunteers ('A1–A3' in Table 20.1) was calculated to be 3.6 ± 0.2 s ($s\text{O}_2 = 0.95$) to 7.0 ± 0.9 s ($s\text{O}_2 = 1.00$). Blood equilibrated with CO was found to have a ^{129}Xe T_1 of 7.9 ± 0.1 s, in good agreement with the highest T_1 value of 7.8 s measured in fully oxygenated blood. (NB: The T_1 values quoted above correspond to signal data from ^{129}Xe in RBCs (equally we could have quoted the ^{129}Xe –plasma T_1 s) at 1.5 T.)

The ^{129}Xe relaxation rate in isolated plasma, $1/T_{1,b}$, was found to increase linearly with increasing dissolved O_2 concentration, as predicted by eqn (20.15), which was fitted to the data to obtain the ^{129}Xe – O_2 relaxivity in plasma, $r_{\text{O}_2} = 0.075 \text{ s}^{-1} \text{ mM}^{-1}$, and the ^{129}Xe spin-lattice relaxation rate in isolated plasma in the absence of molecular oxygen, $1/T_{1,b}^0 = 0.046 \text{ s}^{-1}$ ($T_{1,b}^0 = 21.7$ s) – see Figure 20.3, (iii). The concentration of O_2 in plasma within whole blood can be calculated by using the relationship $[\text{O}_2] = p\text{O}_2 \delta_{\text{wb}}$ with a previously measured O_2 –plasma solubility coefficient (for whole blood), $\delta_{\text{wb}} = 1.69 \times 10^{-3} \text{ mmHg}^{-1} \text{ mM}$, assuming an Hb concentration value of 9.3 mM (15 g dL^{-1}) and sample temperature of 20°C .⁵⁶ The highest $p\text{O}_2$ value in whole blood samples used throughout this study was measured to be 133 mmHg, which corresponds to an O_2 concentration of 0.22 mM. One can ascertain, therefore, the contribution of dissolved unbound molecular O_2 to ^{129}Xe relaxation in whole blood to be negligible since for the highest oxygen concentration of 0.22 mM, the relaxation contribution from oxygen, $r_{\text{O}_2}[\text{O}_2] = 0.017 \text{ s}^{-1}$, is significantly smaller than the lowest ^{129}Xe relaxation rate of $1/T_1 = 0.13 \text{ s}^{-1}$ experimentally measured in whole blood equilibrated with CO.

Using the result that the observed ^{129}Xe relaxation rate, $1/T_1$, in whole blood samples is the same in RBCs and plasma over the full blood oxygenation range, it is possible to express the intrinsic ^{129}Xe relaxation rate for xenon dissolved in RBCs, $1/T_{1,a}$, as a function of $s\text{O}_2$, in terms of the earlier derived relaxation constants, by combining eqn (20.16) and (20.18), yielding

$$\frac{1}{T_{1,a}} = \frac{2T_{1,b}^0 \left[\kappa(1 - \exp(r_{\text{O}_2}s\text{O}_2)) + \frac{1}{T_{1,\text{dHb}}} \right] - (r_{\text{O}_2}\delta_{\text{wb}}p\text{O}_2T_{1,b}^0 + 1)}{T_{1,b}^0} \quad (20.19)$$

This relationship is shown graphically in Figure 20.5, (a). Intrinsic relaxation rates for ^{129}Xe in RBCs in fully oxygenated blood, $1/T_{1,a}^{\text{OHB}} = 0.19 \text{ s}^{-1}$, and fully deoxygenated blood, $1/T_{1,a}^{\text{dHb}} = 0.84 \text{ s}^{-1}$, were calculated by setting $s\text{O}_2$ to 1.00 and 0.00, respectively, in eqn (20.19).

20.5.1.1 ^{129}Xe -RBC Relaxation Mechanisms

Evaluation of the relaxation mechanisms contributing to the change in ^{129}Xe relaxation with RBC oxygenation is substantially more complicated than evaluation of the change in ^{129}Xe relaxation due to varying O_2 concentration in plasma, and hence a rigorous, fully quantitative treatment is beyond the scope of this chapter. We do however, herein, expand on the possible relaxation mechanisms. Two relaxation mechanisms are considered: (i) dipole-dipole spin-lattice relaxation from ^{129}Xe -Hb₄ (in the case of deoxyhaemoglobin) and ^{129}Xe - ^1H interactions and (ii) dipole-dipole cross-relaxation of ^{129}Xe to protons at the xenon-Hb binding sites *via* the spin-induced nuclear Overhauser effect (SPINOE).⁵⁷ Both of these mechanisms depend very strongly on the proximity of ^{129}Xe to the neighbouring proton spins and paramagnetic Hb₄,⁵⁸ thus accurate knowledge of the xenon-Hb binding sites is needed to evaluate the relative dipole-dipole and cross-relaxation contributions to the ^{129}Xe relaxation.

As mentioned in Section 20.2.2, the xenon binding sites have recently been located only in the deoxygenated form of haemoglobin. Without knowledge of the locations of xenon atoms in oxyhaemoglobin, it is not possible to accurately estimate the relative changes in dipole-dipole and cross-relaxation interaction strengths.

Despite this, it is possible to make some assumptions in order to gain insight into the mechanisms driving the non-linear change in the ^{129}Xe relaxation rate with blood oxygenation. Let us assume the following: (i) dipole-dipole ^{129}Xe -Hb₄ interactions is the dominant relaxation mechanism (over ^{129}Xe - ^1H dipole-dipole and ^{129}Xe - ^1H SPINOE interactions); (ii) the xenon-Hb binding site locations do not change with blood oxygenation (*i.e.* the ^{129}Xe -heme distances do not change); and (iii) from the findings of Coryell *et al.*,²⁷ the concentration of paramagnetic Hb₄ changes approximately linearly with blood oxygenation. If these assumptions were valid, one would expect to observe a linear change in the ^{129}Xe relaxation rate with blood oxygenation. However, the observation of a non-linear change in ^{129}Xe relaxation rate with blood oxygenation suggests that if dipole-dipole ^{129}Xe interactions with paramagnetic Hb₄ were the dominant relaxation process, the number/location of xenon-Hb binding sites must change with blood oxygenation. Considering ^{129}Xe cross-relaxation to protons, polarisation transfer in SPINOE is most rapid when xenon is temporarily bound, thus if the xenon-Hb binding sites do indeed change with blood oxygenation, one would expect a concomitant change in the ^{129}Xe - ^1H cross-relaxation rate. As highlighted above, knowledge of the xenon-Hb binding sites in oxyhaemoglobin is crucially required before attempting a quantitative description of the complicated underlying relaxation mechanisms responsible for the change in ^{129}Xe relaxation with blood oxygenation.

20.5.2 ^{129}Xe Exchange in Whole Blood

The measured ratios of ^{129}Xe -plasma to ^{129}Xe -RBC magnetisations were used to calculate xenon-RBC and xenon-plasma of residency times/exchange rates (eqn (20.5) and (20.6)) and xenon plasma-RBC partition

Table 20.2 Ratio of ^{129}Xe -plasma magnetisation to ^{129}Xe -RBC magnetisation, M_b/M_a ; residency times, τ_b and τ_a , and exchange rate constants, k_b and k_a , for xenon in plasma and RBCs; and calculated xenon plasma–RBC partition coefficients, δ_b/δ_a , for three haematocrit (HCT) values. All values presented in the table correspond to whole blood samples at a temperature of 20 °C.

HCT	M_b/M_a	τ_b/ms	k_b/ms^{-1}	τ_a/ms	k_a/ms^{-1}	δ_b/δ_a
0.39	0.56	18.7	0.053	33.5	0.03	0.36
0.48	0.36	16.3	0.061	45.3	0.022	0.33
0.54	0.34	16.1	0.062	47.3	0.021	0.4

coefficients (eqn (20.7)) for a range of HCT values by applying the two-site exchange model presented in Section 20.3.1. The mean xenon plasma–RBC partition coefficient calculated for blood at 20 °C over an HCT range of 0.39 to 0.54 was calculated to be 0.36 ± 0.04 , which is in reasonable agreement with the xenon plasma–RBC partition coefficient of ≈ 0.3 calculated previously from red cell suspensions at 20 °C by Chen *et al.*⁵⁹ See Table 20.2 for calculated values of residency times/exchange rates and xenon plasma–RBC partition coefficients.

20.6 ^{129}Xe Chemical Shift Dependence on Blood Oxygenation

20.6.1 ^{129}Xe Chemical Shift Mechanisms

The resonance frequency of ^{129}Xe in solution is determined by the local magnetic field experienced at the nucleus, which is characterised by the chemical shift screening or shielding constant, σ :

$$\omega_{\text{obs}} = \gamma B_{\text{eff}} \quad (20.20)$$

$$B_{\text{eff}} = (1 - \sigma)B_0 \quad (20.21)$$

$$\omega_{\text{eff}} = \gamma(1 - \sigma)B_0 \quad (20.22)$$

where ω_{obs} is the observed resonance frequency, γ the gyromagnetic ratio, B_0 the applied field and B_{eff} the effective field at the nucleus. As proposed by Buckingham *et al.*⁶⁰ the screening term can be partitioned into:

$$\sigma = \sigma_a + \sigma_e + \sigma_w + \sigma_b \quad (20.23)$$

where σ_a is a contribution from molecular anisotropy effects, σ_e the polar effect caused by an electric field, σ_w due to the van der Waals forces between the solute and solvent and σ_b indicates the shielding arising from bulk magnetic susceptibility effects. $\sigma_b < 0$ for a paramagnetic susceptibility, leading to an increase of B_{eff} and hence ω_{eff} . For ^{129}Xe dissolved in solution at body temperature, the anisotropic and electric field terms are zero⁶¹

leaving only the bulk susceptibility and van der Waals terms to contribute to the shielding constant.

As already mentioned in Section 20.2.1, oxyhaemoglobin is known to be diamagnetic ($\sigma_b > 0$), whereas deoxyhaemoglobin, with two unpaired electrons, has a significant paramagnetic moment ($\sigma_b < 0$). Thus, as RBC oxygenation increases, σ_b also increases and should result in a decrease in B_{eff} and a concomitant decrease in ω_{obs} . However, the chemical shift observed in the data presented here moves towards higher resonance frequencies with increasing oxygenation, opposite to that expected if bulk susceptibility were the principle mechanism. This observation is in agreement with previous results, suggesting that the frequency shift in dissolved ¹²⁹Xe is dominated by the van der Waals shielding contribution, σ_w .⁶²

Stephen⁶³ has demonstrated that the van der Waals deshielding experienced by a nucleus within a solvent is proportional to the mean square electric field, $\bar{F}^2$, at that nucleus brought about by fluctuations among the electrons located on the neighbouring solvent molecules, *i.e.*:

$$-\sigma_w = \xi \bar{F}^2, \quad (20.24)$$

where ξ , referred to by Jameson and de Dios⁶⁴ as the ‘shielding hyperpolarisability’, is large for ¹²⁹Xe, whose nucleus is surrounded by a large, easily deformed electron cloud. As a result of this high hyperpolarisability, the chemical shift of dissolved ¹²⁹Xe in a solvent is very sensitive to small differences in the dispersion fields acting with liquid solvents.

The approach commonly used in past attempts to correlate solvent-induced ¹²⁹Xe chemical shifts with $\bar{F}^2$ is to use a continuum model to describe the solvent.^{65,66} Specifically, the mean square field, $\bar{F}^2$, is equated to the square of the square of the Bayliss-McRae function⁶⁶ – $\bar{F}^2(n) = (n^2 - 1)/(2n^2 + 1)$ – where n is the index of solvent refraction. More recently, Lim *et al.*,⁶⁷ studying the chemical shifts of ¹²⁹Xe in liquid haloalkanes showed a linear proportionality between the ¹²⁹Xe van der Waals shielding constant, σ_w , and the solvent refraction density, $\rho^R = (n^2 - 1)/(n^2 + 2)$. The refractive indices of oxyhaemoglobin and deoxyhaemoglobin have been recently measured in a study conducted by Zhernovaya *et al.*,⁶⁸ where no significant difference between the refractive index of deoxygenated and oxygenated haemoglobin was reported within the visible range of the spectrum; the observed ¹²⁹Xe–RBC chemical shift change with blood oxygenation cannot, therefore, be predicted using the whole blood refractive index.

Experiments using Mössbauer spectroscopy⁶⁹ suggest that the electron cloud of haemoglobin is drawn towards the highly electronegative oxygen molecule in oxyhaemoglobin, but is more evenly distributed in deoxyhaemoglobin. As ¹²⁹Xe forms transient van der Waals bonds with haemoglobin, the net electron cloud is likely to become more distorted and pulled away from the ¹²⁹Xe nucleus while it is bound within the more electronegative oxyhaemoglobin state. This would act to reduce the van der

Waals shielding, σ_w , and would generate a shift to higher dissolved ^{129}Xe resonance frequency, in agreement with the observed data. In addition to changes in the electronegativity of the haemoglobin molecules with blood oxygenation, the binding sites and locations of xenon may be changing as the haemoglobin makes transitions between the oxy and deoxyhaemoglobin state. As the extent of the shielding constant σ_w is strongly dependent on the separation between a nucleus and the molecules giving rise to fluctuating electric fields,⁶⁴ changes in position would greatly alter the magnitude of the mean square field, F^2 , experienced by the xenon nucleus within haemoglobin. As mentioned in Section 20.2.2, xenon binding sites have been comprehensively identified in deoxyhaemoglobin, but are yet to be located within oxyhaemoglobin; until the locations of xenon binding sites have been determined in both forms of haemoglobin, a full theoretical description of the ^{129}Xe chemical shift changes with blood oxygenation is not possible.

20.6.2 ^{129}Xe Chemical Shift vs. Blood Oxygenation

20.6.2.1 In vitro Experiments

In previous studies at a field strength of 1.5 T, the ^{129}Xe chemical shift in RBCs was found to increase non-linearly with blood oxygenation⁷⁰ – see Figure 20.6, (c). We have recently observed at 1.5 T and 3 T a similar non-linear increase in the ^{129}Xe –RBC chemical shift over a similar oxygenation range. In our recent studies, the ^{129}Xe chemical shift in plasma remained fixed in frequency over the whole blood oxygenation range. Using the ^{129}Xe –plasma resonance as a 0 ppm reference, we found the ^{129}Xe –RBC chemical shift to increase from 20.5 ppm in approximately fully deoxygenated blood ($s\text{O}_2 = 0.06$) to 26 ppm in fully oxygenated blood ($s\text{O}_2 = 1.00$) – see Figure 20.6, (d). This observed chemical shift vs. oxygenation behaviour is consistent when the same experiment is performed at magnetic field strengths of 1.5 T and 3 T, indicating it is a field strength-independent effect. To quantify the change in RBC–plasma peak separation, δ , as a function of blood oxygenation in our study, the peak ^{129}Xe –RBC and ^{129}Xe –plasma locations, δ_r^0 and δ_p^0 , were determined by fitting absorption spectra, $\text{Re}[S]$, to a linear combination of two Lorentzians

$$\text{Re}[S](\delta) = A_r \frac{\frac{1}{2} \Gamma_r}{(\delta - \delta_r^0) + \left(\frac{1}{2} \Gamma_r\right)^2} + B_p \frac{\frac{1}{2} \Gamma_p}{(\delta - \delta_p^0) + \left(\frac{1}{2} \Gamma_p\right)^2} \quad (20.25)$$

where A_r and B_p are the amplitudes of the RBC and plasma ^{129}Xe resonances; and Γ_r and Γ_p are the FWHMs of the two peaks – see Figure 20.6 (a). The extracted data were fitted to an empirical equation

$$\Delta\delta(s\text{O}_2) = \alpha \exp(\beta s\text{O}_2) + \delta_0, \quad (20.26)$$

where $\Delta\delta$ is the RBC–plasma peak separation, α is a scaling constant, β is an empirical screening constant and δ_0 is the RBC–plasma peak

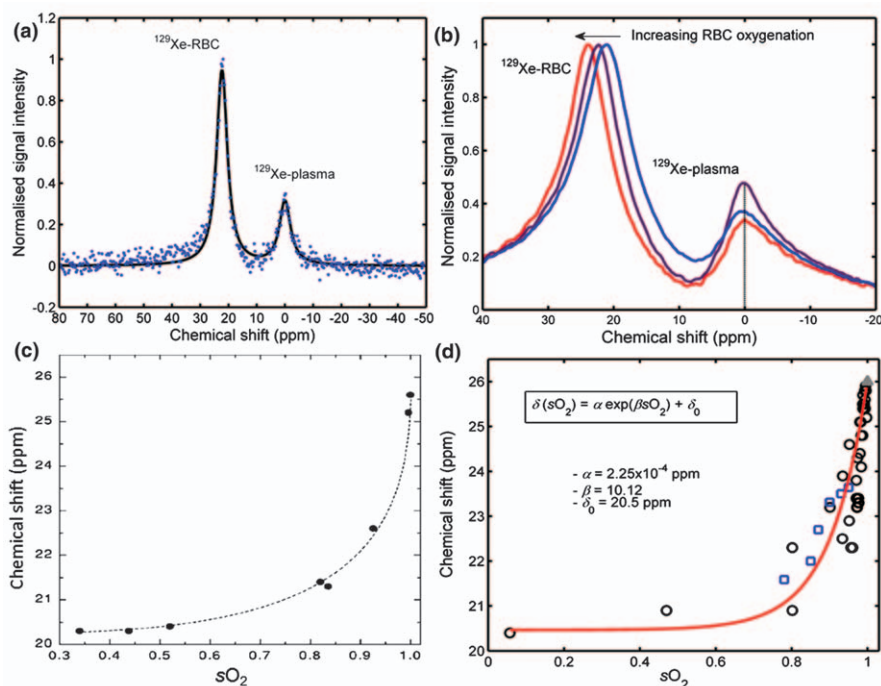


Figure 20.6 (a) ^{129}Xe -blood spectrum at 1.5 T. The absorption spectrum was fitted to a linear combination of two Lorentzians to determine of peak positions. (b) 3 T ^{129}Xe -blood spectral peaks. With increasing oxygenation, the peak associated with ^{129}Xe dissolved in RBCs is seen to shift measurably towards higher resonance frequency. (c) The separation between the ^{129}Xe -RBC peak and the ^{129}Xe -plasma peak plotted against the measured blood oxygen saturation, $s\text{O}_2$, measured by Wolber *et al.*⁴⁸ at 1.5 T. (d) ^{129}Xe -RBC chemical shift vs. $s\text{O}_2$ measured recently at two field strengths: black open circles and blue open squares are from measurements at 1.5 T and 3 T, respectively. The red line is a fit to the data using eqn (20.26) and the grey triangle represents blood equilibrated with carbon monoxide (simulating fully oxygenated blood). (c) Taken from ref. 70 with permission. Copyright 2000 by John Wiley and Sons.

separation in fully deoxygenated blood – see Figure 20.6, (d) for the fitted function.

The observation of a non-linear dependence of ^{129}Xe -RBC chemical shift on blood oxygenation in previous work⁷⁰ over a similar ^{129}Xe chemical shift range lead the authors to the hypothesis that this effect was a result of the co-operative binding mechanism of haemoglobin,^{40,71} conformational changes of the haemoglobin molecule after binding of each oxygen molecule would be expected to inhibit the ability of xenon to bind at its normal sites (see ref. 39 and Figure 20.1, (a1) and (a2) for xenon-haemoglobin binding sites).

As mentioned in Section 20.2.1, Coryell²⁷ found the bulk susceptibility of haemoglobin to change linearly as a function of sO_2 , despite the conformational changes in the protein³⁹ caused by co-operative binding. In addition, it was shown that a single haemoglobin molecule has the highest probability of being in one of the two states of extreme oxygen saturation. At half saturation ($sO_2 = 0.50$), haemoglobin with 1–3 bound oxygen molecules comprises only a third of the total population, with the bulk of the haemoglobin molecules being in one of two states – either completely saturated with 4 bound oxygen molecules, or desaturated with 0 bound oxygen molecules.²⁷ The net oxygen saturation, and thus the net magnetic susceptibility, is the ensemble average for the entire population. Furthermore, as noted previously,⁷⁰ the size of the observed ^{129}Xe –RBC chemical shift is larger than that plausibly caused by a difference in bulk magnetic susceptibility between the two extreme oxygenation states. Therefore, an alternative mechanism to bulk susceptibility changes in haemoglobin must be driving the observed change in ^{129}Xe –RBC chemical shift. To help determine whether the underlying mechanisms driving the change in ^{129}Xe relaxation and ^{129}Xe –RBC chemical shift with blood oxygenation are related, a correlation plot of the variation of the two NMR parameters is shown in Figure 20.7. The plot reveals that changes in ^{129}Xe $1/T_1$ and ^{129}Xe –RBC chemical shift are well correlated ($R^2 = 0.82$). This strongly suggests that the underlying mechanism driving the change is the same. As the chemical shift and relaxation rate of ^{129}Xe in solvents is strongly dependent

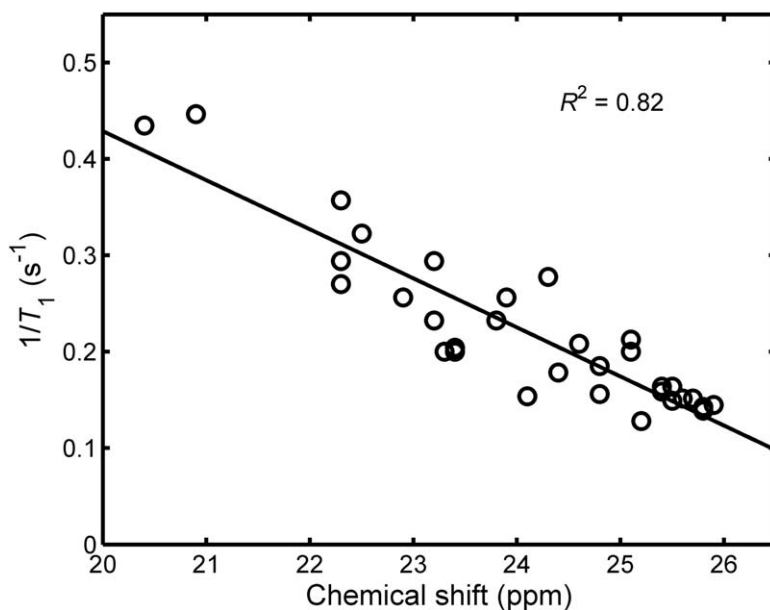


Figure 20.7 Correlation of ^{129}Xe relaxation rate, $1/T_1$, and ^{129}Xe –RBC chemical shift in whole blood samples for a range of blood oxygenations.

on inter-molecular separations, it is likely that the interplay of oxygen and xenon binding at the available sites in the haemoglobin molecule is largely responsible for the observed dependencies of relaxation and chemical shift blood oxygenation.

20.6.3 *In vivo* Lung Experiments

To determine whether the resonance frequency of ^{129}Xe in RBCs could be used *in vivo* as a potential probe for pulmonary blood oxygenation, we have recently acquired preliminary ^{129}Xe –blood NMR spectra during breath-hold apnea, which provides a simple model for pulmonary blood oxygenation modulation.

Figure 20.8, (a) shows a waterfall plot of ^{129}Xe –dissolved spectra acquired as a function of time during breath-hold apnea with a TR of 0.8 s. The ^{129}Xe resonance located at 0 ppm corresponds to ^{129}Xe dissolved in parenchymal tissue and blood plasma (^{129}Xe –TP) and the resonance located downfield is from ^{129}Xe dissolved in RBCs. The ^{129}Xe –TP signal decays monotonically over the breath-hold period. It is assumed that this signal decay follows the T_1 of the ^{129}Xe gas (dominated by the presence of paramagnetic oxygen in the lungs), which acts as a magnetisation reservoir, replenishing the ^{129}Xe –dissolved magnetisation in between RF pulses. Although the ^{129}Xe –RBC signal decays with the same general rate, it does not decay monotonically; instead, it is modulated periodically over the breath-hold time. In order to view this time-modulated decay behaviour more clearly, the ^{129}Xe –RBC signal was normalised to the ^{129}Xe –gas T_1 , which was measured to be 18.8 s, in good agreement with previously measured ^{129}Xe –gas T_1 values of ~ 20 s.⁷² The temporal sampling resolution was increased (TRs = 0.1 s, Figure 20.8, (d) and (e)) and the signal modulation from ^{129}Xe –RBCs was observed to increase in frequency, indicating that at TR = 0.8 s (lower temporal sampling resolution), the modulation was underestimated as a result of undersampling the signal. The ^{129}Xe –TP signal within this temporal resolution was observed to also modulate with the same frequency as the ^{129}Xe –RBC signal. This observation of ^{129}Xe –RBC/TP signal modulation during a breath-hold agrees with results from Ruppert *et al.*⁷³ where a similar modulation was observed during a chemical shift saturation recovery experiment. The peak–peak signal modulation time observed here is within typical heart beat time periods, suggesting that cardiac triggering could be used in future experiments to monitor in real-time the cardiac output to the pulmonary circuit, where abnormal values may indicate cardiovascular pathologies.

The ^{129}Xe –RBC chemical shift decreases by approximately 1 ppm over the breath-hold period (Figure 20.8, (b)), whereas the ^{129}Xe –TP remains fixed in position. As with the ^{129}Xe –RBC signal change, the chemical shift was observed to show a periodic modulation, as shown in Figure 20.8, (c). Eqn (20.26) was used to calculate blood oxygenation values from the measured *in vivo* chemical shift values, where it is estimated that the average pulmonary blood oxygenation decreases by $\sim 3\%$ over the breath-hold.

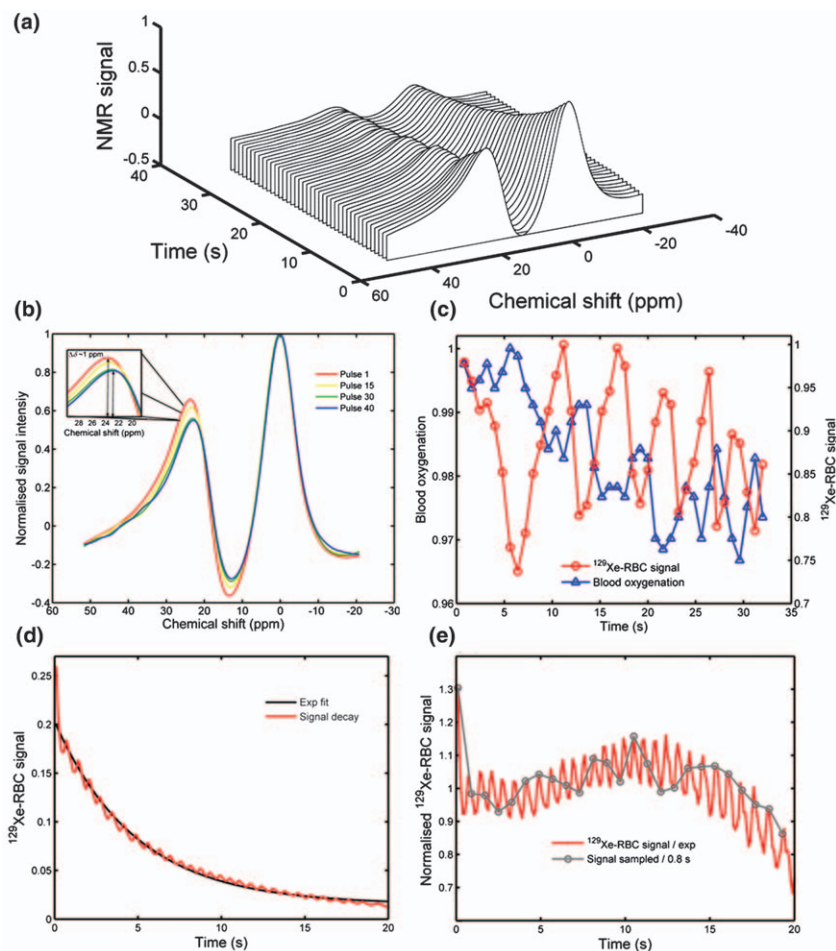


Figure 20.8 (a) A waterfall plot of typical time series *in vivo* lung ^{129}Xe -dissolved spectra. The resonance at 0 ppm is ^{129}Xe dissolved in parenchymal tissue/blood plasma (TP) and the resonance downfield is from ^{129}Xe dissolved in RBCs. Each spectrum was acquired using a flip angle of $\sim 90^\circ$, and a TR of 0.8 s. The decay in both compartments follows approximately the T_1 relaxation (due to the presence of oxygen in the lungs and RF excitation) of the ^{129}Xe -gas, the magnetisation reservoir that acts to replenish the ^{129}Xe -dissolved signal between RF pulses. (b) ^{129}Xe -dissolved spectra at different time points during the breath-hold. The ^{129}Xe -RBC chemical shift decreases by ~ 1 ppm throughout the breath-hold, whereas the ^{129}Xe -TP remains fixed in position. (c) *In vivo* lung blood oxygenation and ^{129}Xe -RBC signal intensity over breath-hold apnea from a healthy volunteer. The blood oxygenation and ^{129}Xe -RBC signal (corrected for ^{129}Xe -gas reservoir decay due to T_1 and RF destruction) oscillate at the same frequency where the blood oxygenation maxima/minima coincide with ^{129}Xe -RBC signal minima/maxima. (d) ^{129}Xe -RBC signal acquired with increased temporal resolution (TR = 0.1 s). Black line is an exponential fit to the signal decay. (e) ^{129}Xe -RBC signal normalised to exponential fit. Grey line represents the signal sampled every 0.8 s.

Measurements of changes in oxygen partial pressure (pO_2) as a function of breath-hold have been done in both animal and human lungs using hyperpolarised ³He MR.^{74,75} It was shown in humans that over short breath-holds (<40 s), the decrease in alveolar pO_2 can be approximated by the linear relationship,

$$pO_2 = p_0 - Rt \quad (20.27)$$

where R is the rate of oxygen decrease and p_0 is the initial pO_2 .⁷⁴ In that study, R was calculated to be 1.9 mbar s^{-1} (1.43 mmHg s^{-1}). Assuming an initial lung pO_2 of 105 mmHg for the volunteers in this study, eqn (20.27) yields, after 30 s of apnea, a pO_2 value of 62 mmHg, which corresponds to an $sO_2 > 0.90$ (from the oxygen haemoglobin dissociation curve shown in Figure 20.3, (ii)), so that the low drop of $\sim 3\%$ sO_2 calculated in this study is physiologically realistic based on these previous alveolar pO_2 measurements using ³He.

As well as providing a potential means of probing lung oxygenation and tissue hypoxia in lung diseases, this ¹²⁹Xe spectroscopy technique may also have applications outside of the lungs. Mazzanti *et al.*⁷⁶ have recently shown that the signal of ¹²⁹Xe dissolved in the brain can be modulated in a manner responsive to stimulus, suggesting that a blood flow/perfusion component is at work. Moreover, dissolved ¹²⁹Xe spectra from the human brain have been successfully acquired,⁷⁷ suggesting that ¹²⁹Xe can be detected in organs quite distal from the point of uptake in the lungs.

20.7 Summary

In this chapter, work concerning the dependencies of ¹²⁹Xe spin-lattice relaxation rate and chemical shift on blood oxygenation has been discussed in detail. Both the ¹²⁹Xe relaxation rate and chemical shift change non-linearly with blood oxygenation, with the highest rate of change observed within the blood oxygenation range 0.90 to 1.00, suggesting that ¹²⁹Xe spectroscopy would be most sensitive to changes in arterial blood oxygenation *in vivo*.

The *in vitro* relationship between ¹²⁹Xe–RBC chemical shift and blood oxygenation has been used to non-invasively probe pulmonary blood oxygenation *via* dissolved ¹²⁹Xe *in vivo* whole-lung spectroscopy experiments conducted during breath-hold apnea at 3 T. Furthermore, ¹²⁹Xe–RBC signal modulation of the order of typical heart beat time periods has been observed, which may be combined with cardiac triggering to monitor real-time cardiac output to the pulmonary circuit, where abnormal signal modulations may indicate cardiovascular pathologies.

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CHAPTER 21

Transverse Relaxation of ^{129}Xe in the Lung

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21.1 Introduction

Respiratory diseases (*e.g.* chronic obstructive pulmonary disease, emphysema and asthma) and lung injury (*e.g.* acute respiratory distress syndrome) are significant contributors to morbidity and mortality and represent a major health care burden. While symptoms can be managed, few cures exist due to a lack of insight into the basic mechanisms of lung disease. Clinical assessment and management of lung disease typically involves both pulmonary function tests (PFTs) (*e.g.* spirometry, blood gases) and imaging techniques. However, PFTs are whole-lung measurements and cannot identify regional deficiencies in lung function, which presumably reduces the sensitivity of PFTs to early injury. Imaging is typically performed using planar X-ray and computed tomography (CT), which can reveal changes in anatomy (*e.g.* lung density) but usually not before clinical symptoms manifest. X-ray imaging methods are insensitive to functional changes such as deficits in gas exchange, perfusion and ventilation, which are expected to occur well before anatomical changes. For this reason, nuclear medicine imaging techniques such as single-photon emission tomography (SPECT) and positron-emission tomography (PET) can be used when functional lung

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

information such as ventilation and perfusion is required. However, nuclear medicine imaging is limited in spatial resolution, lacks specificity, and similar to CT, provides additional radiation dose to the patient.

In contrast to X-ray and nuclear medicine imaging methods, magnetic resonance imaging (MRI) provides an approach for probing lung anatomy and function without the use of ionizing radiation, which may be particularly well suited for tracking the progression and regression of lung disease. However, proton MRI is challenging in the lung due to low proton signal as it contains only approximately 20% soft tissue. This low signal is further diminished by the presence of microscopic magnetic field non-uniformities arising from susceptibility differences at the gas–tissue interface. Furthermore, respiratory motion can be problematic leading to image blurring and other artifacts. More recently, hyperpolarized noble gas MRI has been developed for imaging the lung providing multi-planar spatial resolution rivaling CT imaging and a wide palette of anatomical and functional lung measures. Specifically, hyperpolarized ^3He MRI has been demonstrated to be useful in a variety of lung diseases, including chronic obstructive pulmonary disease (COPD),¹ asthma² and cystic fibrosis.³

Both ^3He (helium-3) and ^{129}Xe (xenon-129) can be hyperpolarized and are useful for clinical lung imaging. Due its larger gyromagnetic ratio, ^3He provides the strongest signal, but is an exceedingly rare by-product of the radioactive decay of tritium and therefore limited in availability. ^{129}Xe is substantially more abundant, relatively inexpensive and although lower in signal compared to ^3He (due to lower gyromagnetic ratio), can be polarized more rapidly and potentially to higher levels.⁴ Owing to its substantially larger atomic size, ^{129}Xe has a self-diffusion coefficient approximately an order of magnitude smaller than ^3He , resulting in differences in measured apparent diffusion coefficients (ADC) and relaxation times in the lung. As well, ^{129}Xe is relatively soluble in tissues, specifically blood, and can thus provide images of tissue beyond the lung space.⁵ Albert *et al.* demonstrated the first MR *in vivo* images derived from a hyperpolarized ^{129}Xe in 1994.⁶ Since that original demonstration, the potential of hyperpolarized ^{129}Xe MRI has been shown for the diagnosis of respiratory diseases including COPD and lung injury in both humans⁷ and animal models.^{8,9} Figure 21.1 shows typical lung MR images obtained in our laboratory with hyperpolarized ^{129}Xe in a human subject and a rat.

Since the available magnetization is non-renewable, careful attention to the hyperpolarized ^{129}Xe MRI method is required to achieve best image quality and extract useful information. In particular, the time constants governing the relaxation of the transverse magnetization (T_2^* and T_2), are important to consider and can provide valuable microanatomical and functional information. This chapter provides an overview of the principal mechanisms of ^{129}Xe transverse relaxation in the gas phase of the lung, including how transverse relaxation times affect lung MRI image quality. The choice of optimal field strength is discussed and the role of low static magnetic fields is highlighted. The application of low field ^{129}Xe gas

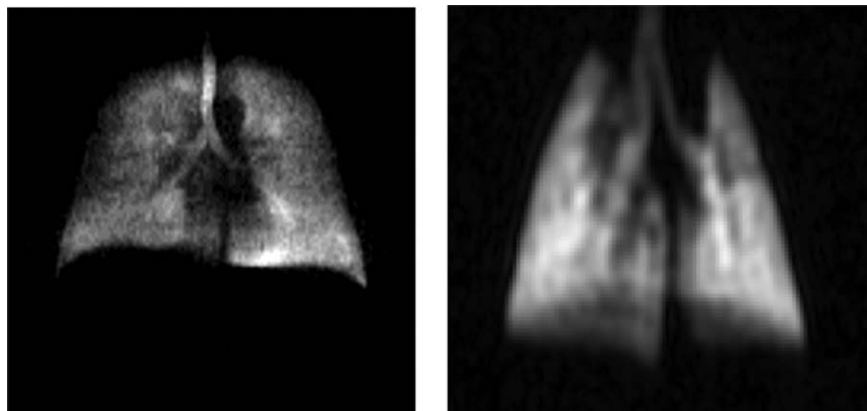


Figure 21.1 Hyperpolarized ^{129}Xe lung images obtained at 3 T in the coronal plane for human (left) at 40 cm field-of-view and for rat (right) at 6 cm field-of-view. The human image is a single 1 cm slice with an in-plane resolution of 3 mm, following inhalation of 500 mL of ^{129}Xe polarized to a level of approximately 10–20%. The rat image is a 2D projection with an in-plane resolution of 0.5 mm, following 5 tidal breaths (~ 4 mL each) of ^{129}Xe polarized to a level of approximately 10–20%.

transverse relaxation times to estimation of ADC and alveolar partial pressure of oxygen (p_{AO_2}) is described and the effects of transverse relaxation of ^{129}Xe occurring in the dissolved phases of the lung (*i.e.* tissue and blood compartments) are discussed.

21.2 ^{129}Xe Transverse Relaxation

Among the two principle relaxation pathways for ^{129}Xe in the lung, spin-lattice (or longitudinal) relaxation and spin-spin (or transverse) relaxation, the latter will be the subject of this chapter. Transverse relaxation refers to the de-phasing of spins which occurs in the transverse plane following excitation of the longitudinal magnetization and is generally described by an apparent relaxation time, T_2^* , which includes all sources of de-phasing. T_2^* of ^{129}Xe in the lung is observed to vary significantly with both instrumental parameters (*e.g.* static magnetic field strength, echo time) as well as *in vivo* conditions (*e.g.* restricted diffusion, oxygenation) and as such provides a rich source of potential contrast in MRI. In this section we will focus on the transverse relaxation of ^{129}Xe in the gas phase in the lung. Later, we will consider the effects of xenon dissolved in the non-gaseous tissue compartments on the lung (*i.e.* lung tissue and blood). Table 21.1 summarizes published values of gas phase ^{129}Xe T_2^* obtained with different methods in both animal and human lungs at various field strengths.^{10–13} The substantially shortened T_2^* at higher field strengths (1.5 T or higher) has significant implications for clinical lung MRI image quality, as will be discussed further in Section 21.3.1, while the increase in T_2^* values with

Table 21.1 ^{129}Xe gas apparent transverse relaxation times (T_2^*) in human and animal lungs.

Field/T	Method	Subject	T_2^*/ms
0.015	Not described	Rat (whole lung) ¹⁰	~ 100
0.074	Simulated	Rat (whole lung) ¹¹	160 (± 11)
	Free induction decay	Rat (whole lung) ¹¹	150
1.5	Multi-echo	Human ¹²	52
1.89	Simulated	Rat (whole lung) ¹¹	28
	Free induction decay	Rat (whole lung) ¹¹	19 (± 6)
2.0	Multi-echo	Guinea Pig (lung) ¹³	16.5 (± 2.8)
3.0	Simulated	Rat (whole lung) ¹¹	9.5 (± 0.6)
	Free-induction decay	Rat (whole lung) ¹¹	8 (± 3)
	Multi-echo	Human ¹²	24

decreasing field strength provides opportunities for lung imaging using considerably weaker magnetic fields with image contrast sensitive to the microanatomical and physiological conditions of the lung.

The apparent transverse relaxation rate ($R_2^* = 1/T_2^*$) of ^{129}Xe gas in the lung is due to several de-phasing mechanisms:^{14,15}

$$R_2^* = R_2 + R_2' + R_{2,\text{susc}} + R_{2,\text{diff}} \quad (21.1)$$

where R_2 is the inherent spin-spin relaxation rate due to dipolar interactions; R_2' is the de-phasing due to static magnetic field inhomogeneities; $R_{2,\text{susc}}$ is the de-phasing due to differences in magnetic susceptibility in the sample and $R_{2,\text{diff}}$ is the de-phasing due to diffusion through differences in magnetic susceptibility. Due to the fast correlation time of the gas spin state, R_2 is expected to be on the order of the longitudinal relaxation rate, $R_1 (=1/T_1)$, and therefore several tens of seconds and can generally be ignored.¹⁵ An exception to this occurs when the three latter right-hand terms in eqn (21.1) are substantially reduced as with rapid spin echo pulse sequences at low magnetic field strengths as will be discussed later in Section 21.4.1. We will next focus on each of the three latter right-hand terms in eqn (21.1).

21.2.1 Static Field Effects

The second term on the right-hand side in eqn (21.1) describes the static de-phasing of the transverse magnetization in the presence of magnetic field inhomogeneities imposed by the MRI magnet, and is given by:

$$R_2' = \frac{\gamma \Delta B_0}{2} \quad (21.2)$$

where ΔB_0 is the static magnetic field inhomogeneity and γ is the gyro-magnetic ratio for ^{129}Xe ($=\text{MHz T}^{-1}$). This term can generally be reduced through efficient magnet design and careful application of additional small magnetic fields to improve uniformity (*i.e.* shimming). The strong magnetic

fields associated with clinical MR imaging make it very difficult to greatly reduce this term to a negligible value; however, this term can more effectively be eliminated through the use of a spin echo, to be discussed later.

21.2.2 Susceptibility-induced Effects

The third term on the right-hand side of eqn (21.1) describes the transverse de-phasing of spins due to varying precession rates between regions with different susceptibility-induced magnetic fields, principally arising from the numerous air-tissue interfaces in the lung:

$$R_{2,\text{susc}} = \frac{\gamma \Delta\chi B_0}{2} \quad (21.3)$$

where $\Delta\chi$ is the average susceptibility difference in the lung and B_0 is the magnitude of the static magnetic field. The large difference in magnetic susceptibility between tissue and air make this effect quite pronounced in the lung ($\Delta\chi \sim 10^{-5}$).¹⁴

21.2.3 Diffusion Effects

The fourth term on the right-hand side in eqn (21.1) describes the additional transverse relaxation due to diffusive motion of nuclei through the susceptibility-induced magnetic field gradients in the lung:¹⁴

$$R_{2,\text{diff}} = \left[\gamma \left(\frac{\Delta\chi}{l} \right) B_0 \right]^2 D \frac{\tau^2}{3} \quad (21.4)$$

where l is the characteristic length over which χ varies by $\Delta\chi$ (typically the alveolar radius), D is the diffusion coefficient and τ is the echo time. In most cases, we can consider the length over which the nuclei diffuse before de-phasing to be much larger than the characteristic length (*i.e.* fast diffusion regime), and the diffusion term can be written as:

$$R_{2,\text{diff}} = (\gamma \Delta\chi B_0)^2 (l^2/D) \quad (21.5)$$

An exception occurs when the de-phasing is refocused, as for example when an echo is generated in the presence of an applied magnetic field gradient and then eqn (21.4) applies, as will be discussed in Section 21.4.1. Since $\Delta\chi$ is strongly dependent on the geometry of the air-tissue interface, R_{2^*} has been shown to depend on the lung volume.^{12,13}

21.3 Field Strength Dependence of ^{129}Xe Transverse Relaxation

Eqn (21.3)–(21.5) indicate that T_{2^*} is strongly dependent on the static magnetic field strength, B_0 . Figure 21.2 shows the measured dependence of ^{129}Xe gas T_{2^*} on field strength for a lung tissue-mimicking phantom

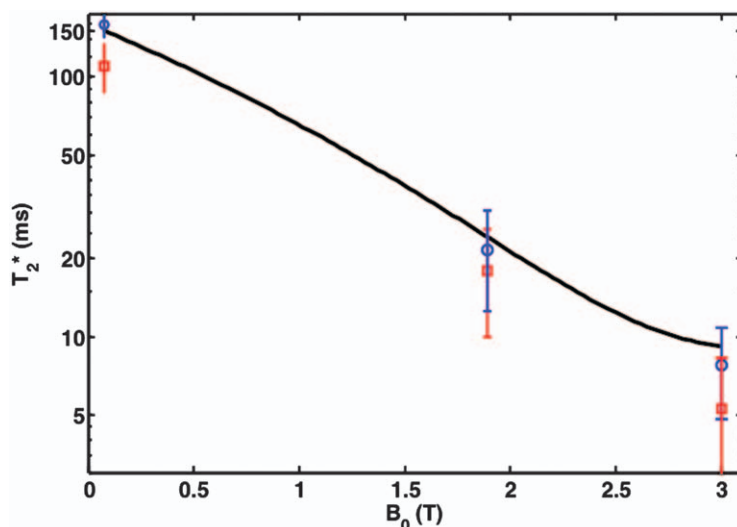


Figure 21.2 Field dependence of ^{129}Xe apparent transverse relaxation time obtained from theoretical simulations (solid line), phantom (square symbols) and *in vivo* rat lungs (circles). Figure reprinted from ref. 11 with permission from Elsevier.

composed of packed gas-filled capillaries in water as well as *in vivo* rat lung.¹¹ Also shown is the theoretical dependence determined by numerical modeling of the transverse relaxation due to susceptibility differences and diffusion in the phantom and the lung. At low field strengths, T_2^* increases to a limit determined by the static field inhomogeneity (eqn (21.2)). At high field strength, T_2^* decreases non-linearly as a function of field (eqn (21.3)–(21.5)) suggesting that ^{129}Xe gas transverse relaxation in the lung is dominated by susceptibility differences between gas and tissue averaged out by diffusion.¹¹

21.3.1 Effect of Field Strength on Lung MRI

Since T_2^* of ^{129}Xe gas in the lung depends strongly on field strength (Figure 21.2), it is an important factor in determining the optimum field strength for MRI, particularly since the magnitude of the hyperpolarized magnetization is field independent. Since T_2^* values at clinical field strengths (1.5–3 T) are on the order of typical MRI signal read-out times (several ms), both image signal-to-noise ratio (SNR) as well as spatial resolution are affected:¹⁶

$$\text{SNR} \propto \text{BW}^{-1/2} \propto (T_2^*)^{1/2} \quad (21.6)$$

$$\Delta x_{T_2^*} = \frac{2}{\gamma G T_2^*} \quad (21.7)$$

These equations assume band-matched conditions and predict that SNR and resolution of clinical hyperpolarized ^{129}Xe lung MRI generally improve as a function of decreasing field strength until an optimum (at approximately 0.1–0.5 T) is reached after which image quality degrades when the image noise becomes dominated by the RF coil, as shown in Figure 21.3.¹⁶

21.3.2 Low Field ^{129}Xe MRI

To the extent that RF coil and electronic noise can be minimized, hyperpolarized ^{129}Xe MRI can be performed at static magnetic field strengths considerable lower than the optimal field shown in Figure 21.2. RF coil and receiver noise can be reduced by a number of approaches, including the use of Litz wire¹⁷ and cryogenic coils¹⁸ as well as superconducting quantum interference devices (SQUIDS). A comparison of SNR between SQUIDS and conventional copper coils can be found in Myers *et al.*¹⁹ Hyperpolarized MRI has been demonstrated at field strengths ranging from a few mT²⁰ to several tens of gauss.^{14,21,22} We have built a resistive MRI system for hyperpolarized ^{129}Xe imaging of rodent lungs at 74 mT.²³ Figure 21.4 shows coronal images obtained from rat lungs demonstrating the improvement in SNR with Litz wire compared to conventional copper wire-wound coils.

21.4 Applications of ^{129}Xe Gas Transverse Relaxation to Measurement of Lung Microanatomy and Function

The use of spin echo sequences effectively eliminates the second term in eqn (21.1). Furthermore, at sufficiently low B_0 , the magnetic susceptibility effects arising from air–tissue interfaces is reduced, such that only the first and last terms on the right-hand side of eqn (21.1) need be considered:

$$R_{2\text{SE}} = R_2 + R_{2,\text{diff}} \quad (21.8)$$

Furthermore, the diffusion term takes the form as shown in eqn (21.4), providing an approach by which one can use $R_{2,\text{diff}}$ to investigate apparent diffusion coefficients (ADC) in the lung with the application of a diffusion-weighted gradient pulse. Furthermore, at sufficiently short echo time (τ) transverse relaxation is dominated by the inherent spin–spin relaxation rate due to dipolar interactions (R_2), which provides a method by which the paramagnetic effects of molecular oxygen can be exploited to estimate alveolar oxygen partial pressure, p_{AO_2} .

21.4.1 Apparent Diffusion Coefficient (ADC)

The signal measured following the application of a magnetic field gradient pulse depends upon ADC according to:

$$S = S_0 \exp[-b\text{ADC}] \quad (21.9)$$

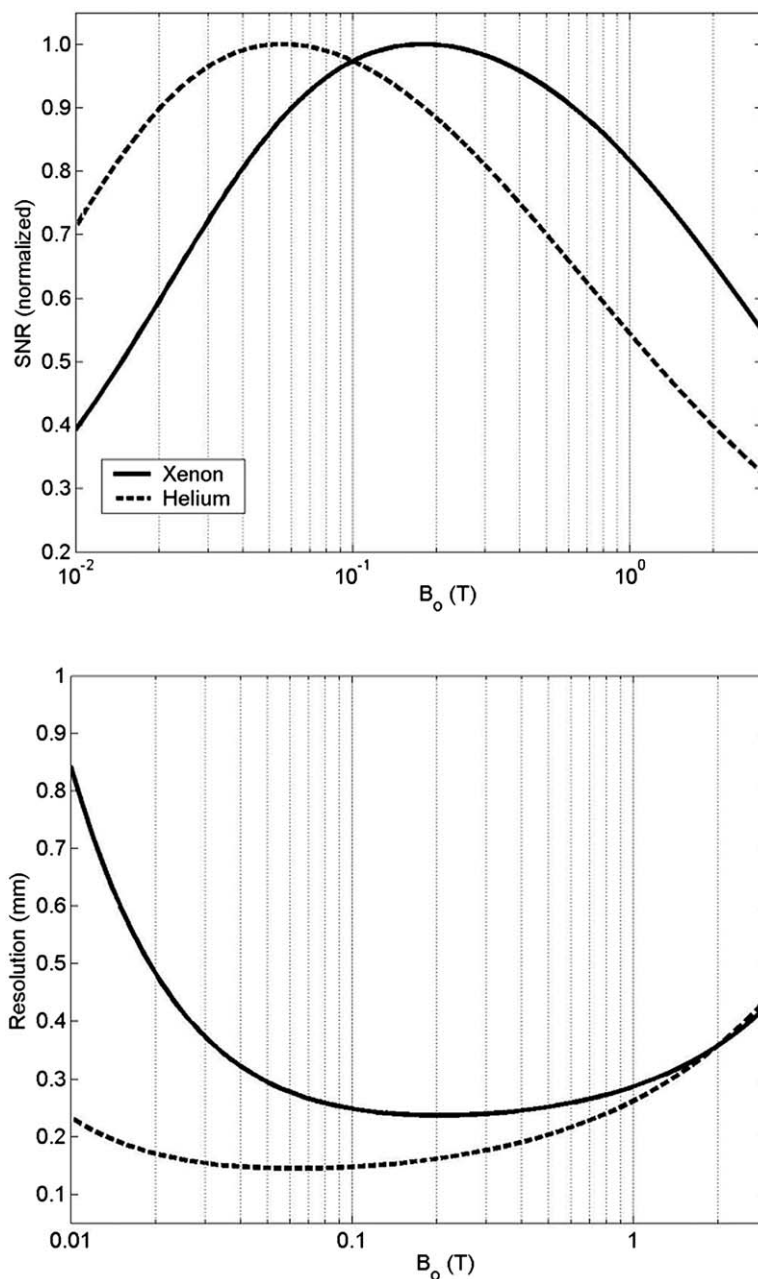


Figure 21.3 Theoretical field strength dependence of clinical hyperpolarized gas image signal-to-noise ratio (a) and spatial resolution for band-matched conditions. Note that optimum image quality is anticipated at intermediate field strengths (0.1 T–0.5 T), significantly lower than typical commercial field strengths (1.5 T–3 T). Figure adapted from Parra-Robles *et al.*¹⁶

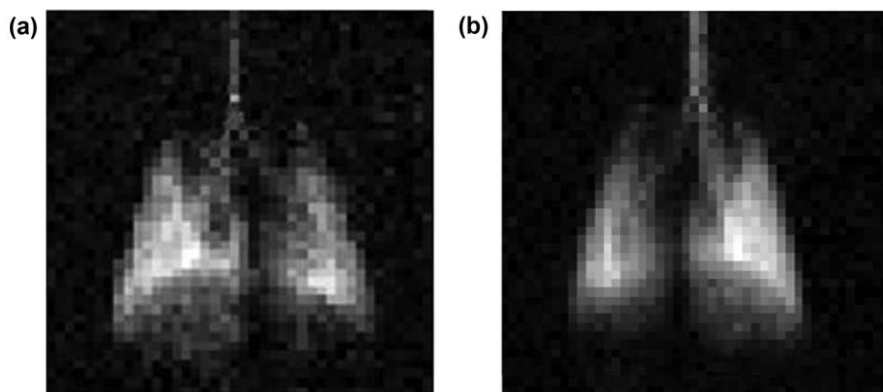


Figure 21.4 Hyperpolarized ^{129}Xe images of *in vivo* rat lungs acquired at 74 mT with (a) conventional copper AWG 18 and (b) Litz AWG 18 type 2 with one diameter spacing between windings. The images are 2D projections with an in-plane resolution of 1.5 mm, following 7 tidal breaths (~ 4 mL each) of ^{129}Xe polarized to a level of approximately 10–20%.

where S_0 is the signal in the absence of the gradient pulse and b is a factor determined by the amplitude and timing of the diffusion-sensitizing gradient pulse, including the period between re-focusing lobes, or diffusion time (Δ). ADC can be estimated by measuring the normalized signal as a function of b value, typically by changing the magnitude of the diffusion-sensitizing gradient pulse as shown in Figure 21.5. In the lung, ADC is strongly dependent on Δ , due to restricted diffusion imposed by the alveolar micro-structure. This makes the ADC exquisitely sensitive to diseases that alter the alveolar size, such as emphysema, as mimicked by elastase instillation in Figure 21.5. The ability to access longer Δ values (~ 100 ms) due to the increased T_2^* at lower fields may also offer an opportunity to increase the diffusive length scale that can be probed.⁸ A more detailed analysis shows that the signal in eqn (21.9) is more adequately modelled by considering anisotropy originating from the cylindrical nature of the terminal airways. This provides a basis for measurement of alveolar and terminal airway sizes, called *morphometry*.^{24,25}

21.4.2 Alveolar Oxygen Partial Pressure (p_{AO_2})

At very low static magnetic field strength (<0.1 T), the transverse relaxation of ^{129}Xe gas provides an opportunity to measure p_{AO_2} in the lung. This approach was first demonstrated using ^3He gas in humans at 3 mT by Bidinosti *et al.*²⁶ using a multi-echo method. Kraayvanger investigated the oxygen dependence of ^{129}Xe spin-spin relaxation measured with a Carr-Purcell-Meiboom-Gill (CPMG) spin-echo pulse sequence at 74 mT, both *in vitro* and *in vivo* in rat lungs (Figure 21.6).²⁷ The *in vitro* results were shown to follow the expected linear dependence:

$$R_{2,\text{CPMG}} = \kappa_2[p_{\text{AO}_2}] \quad (21.10)$$

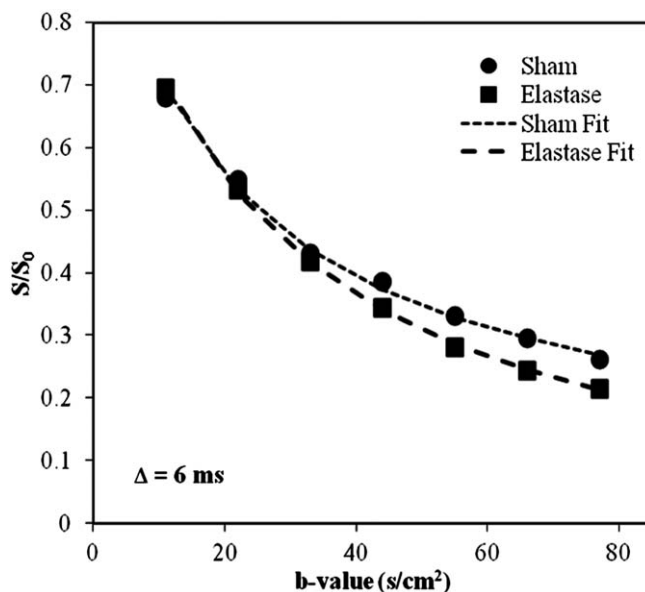


Figure 21.5 Normalized ^{129}Xe spin-echo signals from *in vivo* lung as a function of increasing diffusion-weighting (b value in eqn (21.9)) for representative sham-instilled and elastase-instilled rats at a diffusion time of 6 ms. Note the more significant decay for the elastase rat lungs indicating an increase in apparent diffusion-induced transverse relaxation due to break down of the alveolar walls mimicking emphysema.

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where κ_2 is the spin-spin relaxivity constant in the presence of oxygen, measured to be $7.3 (\pm 0.4) \times 10^{-6} \text{ s}^{-1} \text{ Pa}^{-1}$. Interestingly, the *in vivo* results exhibited multiexponential behavior compared to the *in vitro* results, with one component displaying the opposite trend with increasing wash-in breaths (decreasing $p_{\text{A}}\text{O}_2$) compared to that predicted from eqn (21.10). This behavior was attributed to slow exchange of ^{129}Xe between the gas phase and the dissolved phases in lung tissue, particularly the confounding effects of deoxygenated hemoglobin in blood, as discussed further in the next section.²⁷

21.5 ^{129}Xe Transverse Relaxation in the Dissolved Phase

Perhaps the most unique and exciting feature of hyperpolarized ^{129}Xe is the potential to probe the various dissolved phases (*i.e.* compartments) in the lung. Chemical shift differences permit detection of ^{129}Xe in the gas phase as well as in several dissolved-phase compartments, including the lung

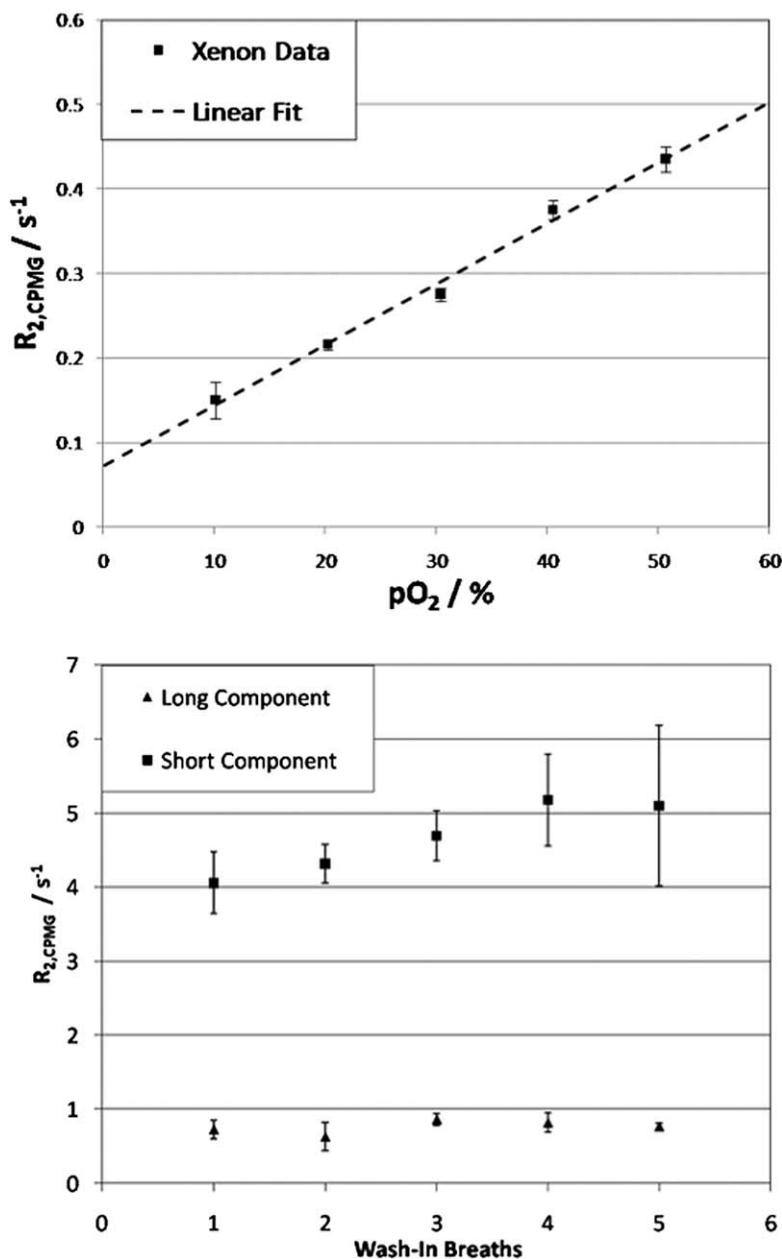


Figure 21.6 ^{129}Xe $R_{2,\text{CPMG}}$ measurements *versus* oxygen concentration *in vitro* (top) and *versus* wash-in breath for *in vivo* rat lung (bottom). Two components of transverse relaxation ($R_{2,\text{short}}$ and $R_{2,\text{long}}$) are observable, with the “short” component dependent on the number of wash-in breaths affecting alveolar oxygen partial pressure ($p_{\text{A}}\text{O}_2$). Figure reprinted from ref. 27 with permission from Wiley.

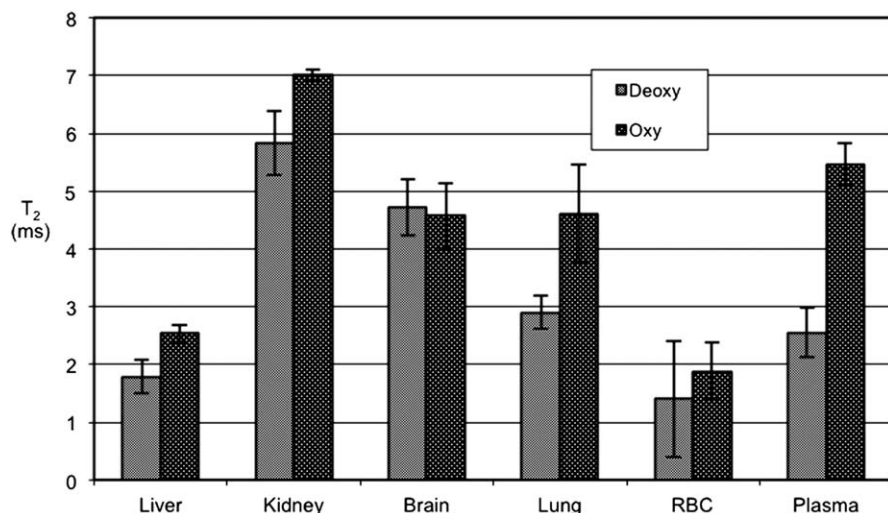


Figure 21.7 Dissolved ^{129}Xe $T_{2,\text{CPMG}}$ measured in tissue homogenates at 9.4 T, for both oxygenated and deoxygenated conditions. The reduction in transverse relaxation times for deoxygenated tissues is likely due to the presence of deoxyhemoglobin, a strong paramagnetic. Figure adapted from Wilson.²⁸

parenchymal tissue and plasma, red blood cells (RBC) and adipose tissue.⁹ Due to the substantially lower diffusion coefficient of ^{129}Xe in the dissolved state (about three orders of magnitude), the mechanisms governing transverse relaxation are anticipated to be different than those in the gas phase. In particular transverse relaxation arising from diffusion through susceptibility-induced gradients is expected to be negligible in the dissolved phase. On the other hand, dipolar interactions arising from binding of ^{129}Xe to paramagnetic deoxyhemoglobin is anticipated to dominate transverse relaxation in blood and well vascularized tissues. Figure 21.7 shows dissolved ^{129}Xe $T_{2,\text{CPMG}}$ relaxation times measured in RBC pellets, plasma and a variety of tissue homogenates at 9.4 T under normal oxygenation conditions as well as deoxygenated.²⁸ The $T_{2,\text{CPMG}}$ values of the dissolved phases are generally a factor of two to three less than the gas phase and demonstrate significant decreases with deoxygenation. As expected, $T_{2,\text{CPMG}}$ of the RBC pellet demonstrates the lowest $T_{2,\text{CPMG}}$ values due to the high concentration of hemoglobin. The other tissues exhibit higher $T_{2,\text{CPMG}}$ values presumably due to the reduced amounts of hemoglobin (*e.g.* plasma) and/or or vascularization. Measurements of linewidth as a function field strength in plasma and perfluorocarbon emulsions (Figure 21.8) suggest that fast exchange of ^{129}Xe between sites of different chemical shift (*i.e.* chemical exchange) may also play an important role in transverse relaxation of dissolved ^{129}Xe .²⁹

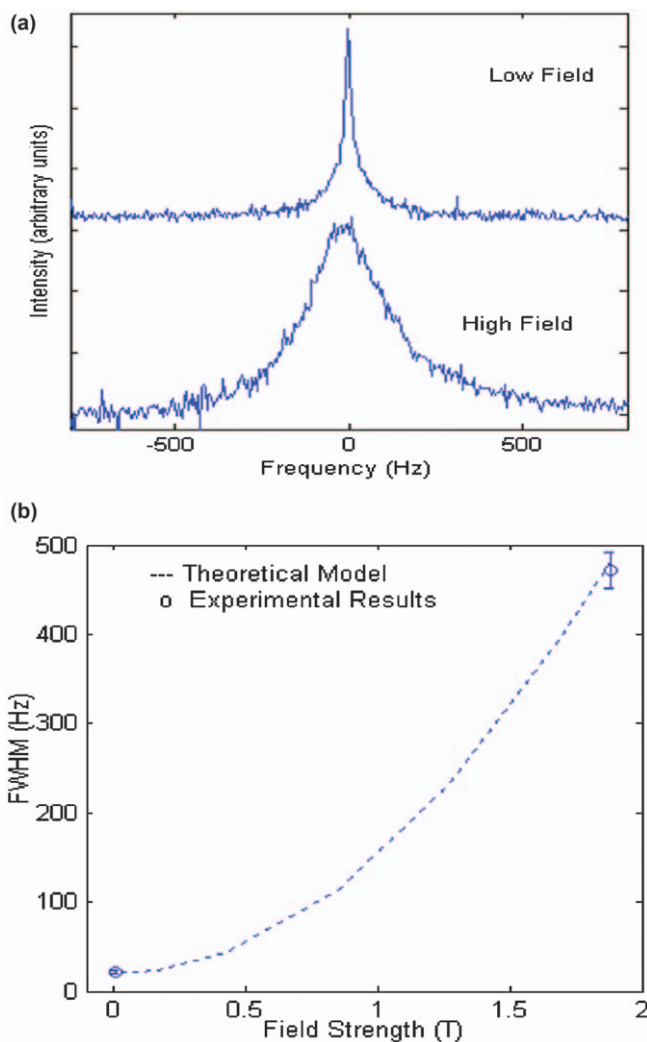


Figure 21.8 (a) Lineshapes of ^{129}Xe dissolved in perfluorocarbon emulsions at 8.5 mT (top) and 1.89 T (bottom). (b) Corresponding linewidths (proportional to $1/T_2^*$) as a function of field strength. Also shown in (b) is the theoretical dependence based on a fast two-site model of chemical exchange.²⁹

21.6 Summary

Hyperpolarized ^{129}Xe MRI is a very promising tool for the investigation of lung disease, particularly to follow longitudinal changes in lung function and anatomy without the accumulated radiation dose associated with X-rays. The apparent transverse relaxation of ^{129}Xe gas (T_2^*) is important in affecting

lung MRI quality and depends strongly on diffusion through susceptibility differences at the air–tissue interface which scale with magnetic field strength. The large increase in T_2^* with decreasing static magnetic field strength (<1 T) permits MRI using magnets considerably weaker than those used conventionally. In addition to advantages associated with reduced cost and complexity, low field MRI T_2 contrast is affected by a variety of mechanisms that can be exploited to characterize microanatomical and functional changes in the lung.

Acknowledgements

Thanks to the Santyr laboratory for scientific contributions over the years, especially Mathieu Boudreau, Albert Cross, William Dominguez-Viqueira, Ryan Kraavanger, Mihai Gherase, Alexei Ouriadov, Juan Parra-Robles, Julia Wallace, Greg Wilson and Peggy Xu. Thanks also to Chris Bidinosti for fruitful discussions.

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Magnetic Resonance Imaging of the Brain using Hyperpolarized ^{129}Xe

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22.1 Introduction

The use of laser-polarized xenon-129 (^{129}Xe) (henceforth referred to here as hyperpolarized (HP) ^{129}Xe) as a novel contrast agent for magnetic resonance imaging (MRI) is quite useful for imaging the lungs and other organs such as the brain. From the earliest days of HP ^{129}Xe MRI, the original interest of co-inventor, Dr Mitchell Albert, was to use ^{129}Xe to better understand the brain and directly image the effect of anaesthesia on brain function. Since xenon is a known anaesthetic and 26% of naturally abundant xenon isotopes are spin 1/2 nuclei (*i.e.*, ^{129}Xe), it was a logical choice to study the effects of anaesthesia on the brain using MRI. Furthermore, xenon readily dissolves into tissue and blood allowing it to travel to other organs in the body, including the brain. The pertinent physics necessary for performing HP gas nuclear magnetic resonance (NMR) and MRI existed long before its application to lung imaging by Albert *et al.* in 1994.¹ Non-equilibrium

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

polarization of ^{129}Xe is typically achieved using the method of spin exchange optical pumping (SEOP) enabling signal enhancements of over 100 000 times above conventional polarization levels. These techniques have been reviewed extensively (see Chapters 3–6).^{2–5} In this chapter, we will briefly review some historical advancements for functional brain imaging such as functional magnetic resonance imaging (fMRI), and then concentrate on discussing the practical considerations and possible delivery methods for using HP ^{129}Xe to image the human brain using magnetic resonance. A more thorough review of conventional fMRI can be found in various fMRI textbooks (*e.g.*, Heuttel, Song and McCarthy). Finally, some basic ground-work and recent literature in the development of brain imaging using HP ^{129}Xe in animals and humans will be discussed.

22.2 Conventional Brain Imaging

The desire to map out the human brain and identify the structures responsible for perception, cognition and motor control has been a long standing goal in the field of neurology and neuroscience. Early work involved invasive methods where researchers physically damage certain locations of the brain in animal models to observe the animals' behavioural changes or lack thereof. Brain mapping has become far more advanced with the advent of positron emission tomography (PET) and MRI; two non-invasive imaging techniques capable of measuring correlates of brain function. PET was the first imaging modality employed to study brain function using radioactive tracers such as fluorodeoxyglucose ($^{18}\text{F}[\text{FDG}]$).⁶ Regions of the brain exhibiting strong metabolic activity could be detected as the tracers emit positrons from the sites of strong metabolism and hence are localized by detection of coincident photons from the positron annihilation. The increased demand for energy at the sites of neuronal activation is responsible for summoning larger quantities of nutrients (glucose and oxygen) which in turn are detected due to radio-labelled ^{18}F delivered to the brain. Though useful for a wide range of applications, PET lacks the ability to image the brain at high resolution, and due to the slow nature of the image acquisition, PET is not well suited for capturing short term physiological processes. MRI on the other hand, is a versatile imaging modality that does not require the use of ionizing radiation (or radioactive tracers) to produce signals for image formation. MRI was later used for brain imaging to study structure employing T_1 and T_2 weighted images that bring out contrast between gray matter, white matter and fluids. These studies were clinically very useful, especially following the findings of Damadian *et al.*⁷ regarding the differences in relaxation times of normal tissues compared to tumours. Like PET, MRI can also be used to study correlates of brain function (fMRI). Using fMRI, researchers have the ability to superimpose maps of 'brain function' onto high resolution proton images of the brain to spatially identify regions of brain activation. fMRI is made possible due to the discovery of the blood oxygen level dependent (BOLD) contrast

mechanism discovered by Seiji Ogawa⁸ and advancements by Belliveau *et al.*⁹ fMRI takes advantage of two physiological mechanisms to produce BOLD contrast in MRI images: (i) changes in blood flow to different regions of the brain in response to neuronal activity and (ii) the range of magnetic susceptibility of hemoglobin which depends on the number of bound oxygen molecules, and is responsible for generating differential T_2^* contrast. It was demonstrated by Ogawa *et al.*⁸ in rats breathing gas mixtures with varying concentrations of oxygen that low oxygenation levels (deoxyhemoglobin) appeared dark and regions of high oxygenation (oxyhemoglobin) appeared bright. Modern fMRI experiments utilize high resolution structural images of the brain paired with high temporal resolution (course spatial resolution) images to detect changes in BOLD contrast. During the fMRI experiment a brain response is evoked in a human subject through the use of a visual stimulus, motor activities or responses to simple questions. Brain signal increases due to BOLD contrast as the oxygenated blood supply displaces deoxyhemoglobin, eliminating signal suppression due to its paramagnetic nature. fMRI offers a valuable tool for the study of brain function and is widely used in the field of neuroscience; however, scan times are often long due to the need to produce statistical maps to detect statistically significant changes in BOLD contrast, which in turn are related to brain function. ^{129}Xe was initially detected in humans and animals in 1997 by Mugler *et al.*¹⁰ and Swanson *et al.*¹¹ demonstrating the feasibility of delivering HP ^{129}Xe via the lungs and detecting it in the brain. Novel techniques have been proposed using HP ^{129}Xe MRI serving as a one shot contrast agent for evaluations of ^{129}Xe wash-in and wash-out effects in humans,¹² and stroke (perfusion)¹³ and brain function¹⁴ in animals.

22.3 Hyperpolarized ^{129}Xe MRI

Though the idea of ^{129}Xe MRI of the brain has existed for over two decades, its development and application for successfully imaging the brain have only become recently possible. Development of HP gas technology and applications for the last two decades were mainly focussed on using ^3He for lung imaging due to the ease of polarizing ^3He to high levels (40–50%) and in clinically relevant quantities. Though some preliminary spectroscopy and imaging of the brain has been attempted,^{10–12} ^{129}Xe brain imaging did not develop quickly and is only now being revisited. With the development of high throughput ^{129}Xe polarizers, capable of producing highly polarized gas,^{15–18} substantial progress in the development of imaging techniques using ^{129}Xe for detecting correlates to brain function can be achieved. The practical considerations for using ^{129}Xe for lung and brain imaging include the physical and chemical properties of xenon, the experimental variables the researcher has at their disposal (*i.e.*, choices in equipment and study parameters) and most importantly, patient safety with regards to xenon consumption.

22.3.1 Physical and Chemical Properties of Xenon

^{129}Xe is a spin 1/2 isotope of xenon, possessing a fully occupied outer electron shell, and is the heaviest of the stable noble gases. Though chemically inert, xenon's large electron shell makes it very sensitive to its local environment becoming distorted and polarized creating a dipole which enables interactions with proteins. Shielding effects also enable a large range of beneficial chemical shifts over the range of 250 ppm. Chemical shifts of note can be seen in Table 22.1 and a more comprehensive list can be found in Miller *et al.*¹⁹ These chemical shifts are also functions of temperatures and density.²⁰

The utility of these distinct resonances enables the detection and localization of ^{129}Xe within these different chemical environments and through the use of specialized acquisition techniques such as Chemical Shift Saturation Recovery (CSSR),^{21–28} Xenon Transfer Contrast (XTC)^{29–32} or Chemical Exchange Saturation Transfer using HP nuclei (HyperCEST),^{33,34} can enable the study of ^{129}Xe exchanging between environments such as gas and tissue in the lung or plasma, brain parenchyma or xenon biosensors.

The solubility of ^{129}Xe in different compounds and tissues is a major limiting factor in the detection of dissolved phase ^{129}Xe ; as it is typically low in biological applications. For example, the Ostwald solubility coefficients for ^{129}Xe dissolved in tissue and RBCs are 0.11 and 0.17 respectively.⁵ Consequently, low solubility poses a major drawback for delivery of ^{129}Xe *via* the lung after inhalation (see xenon delivery section below).

When blood circulation is the vehicle for ^{129}Xe delivery to other organs in the body such as the brain, relaxation of ^{129}Xe magnetization must be carefully considered. Due to the hyperpolarized nature of ^{129}Xe in this work, T_1 relaxation is a decay process acting to depolarize ^{129}Xe which consequently reduces the available signal to perform an image before ^{129}Xe can reach its target. For ^{129}Xe gas in biological systems such as the lung, relaxation times vary with field strength and local conditions (*e.g.*, susceptibility differences). T_1 's between 20–30 s at 3 T have been reported.³⁵ T_2^* has been reported to be around 20 ms at 3 T within the human lung.³⁶ T_2^* values at different lung inflation states at 1.5 T and 3 T have also been

Table 22.1 Listing of chemical shifts of note related to lung, brain and ^{129}Xe biosensors imaging. Chemical shifts are listed relative to the gas phase of ^{129}Xe .

Solvent	Chemical shift (ppm)
Red blood cells	212
Lung pyrenchyma	197
Water	196
Rat head	194.5
Intralipid 30%	194.5
PFOB	106
Cryptophane-A	79

reported with values of 24 ms and 18 ms for partially inflated lungs and 52 ms and 24 ms for fully inflated lungs.³⁷ Robles *et al.* report theory and measurements demonstrating the reduction in T_2^* as a function of field strength ranging between 0.074 T to 3 T,³⁸ and Fox *et al.* report T_2^* in rat lungs to be as short as 2–5 ms at 3 T using an insert gradient optimized for small animal imaging.³⁹ Similarly, T_2^* of dissolved phase ^{129}Xe in the lung is also relatively short (<2 ms at 3 T).⁴⁰ Similar to fMRI BOLD contrast, when ^{129}Xe is dissolved and bound to hemoglobin within red blood cells, T_1 relaxation becomes a function of oxygen concentration. Several studies have been performed by Albert *et al.* and Bifone *et al.* investigating the T_1 relaxation rates of ^{129}Xe in blood.^{41–44} Paramagnetic oxygen is known to contribute to fast T_1 decay of HP ^{129}Xe in the gas phase (*e.g.*, in the lung) and in aqueous and organic solvents. Paradoxically, high levels of blood oxygenation actually lengthens the T_1 of dissolved ^{129}Xe which implies that blood should be highly oxygenated when using blood circulation as a natural delivery agent for ^{129}Xe . Early studies investigating the T_1 of dissolved ^{129}Xe in blood reported inconsistent results.^{43,45} Further studies were able to clear the confusion and reconciled the inconsistencies in reported relaxation times, and also reported oxygen dependent trends (with T_1 's of 3–4 seconds and 6–13 s for deoxygenated and oxygenated blood, respectively).^{41,42,44,46} Wolber *et al.* also demonstrated that T_1 was a non-linear function of oxygenation after measuring T_1 over a range of sO_2 values and suggested that the observed T_1 was not primarily due to interaction with paramagnetic heme groups but was also conformation based.⁴⁴ Oxygenation not only played a role in determining the value of T_1 for ^{129}Xe in blood, but it was also demonstrated in another study that oxygenation also gives rise to a chemical shift which is independent of blood flow.⁴⁷ This information could be exploited to better understand the mechanisms of the BOLD response, which is affected simultaneously by both cerebral blood flow and oxygenation level.

Magnetic field strength is an important factor in ^{129}Xe brain imaging, as relaxation and chemical shift are both dependent on it. Typical field strengths available for human brain imaging are 1.5 T, 3 T and 7 T. There is a lot more flexibility in magnets when it comes to animal studies and imaging has been performed at field strengths as high as 9.4 T.⁴⁸ As field strength increases, T_1 relaxation and chemical shift improves, however, these benefits come at the price of requiring more complicated RF hardware (especially at ultra high fields), higher RF energies (with higher Specific Absorption Rate [SAR] implications) and shortened T_2^* due to magnetic susceptibility and other effects. Though proton fMRI benefits from higher fields yielding better contrast for both large and small vessels, it remains to be seen if high fields are also beneficial for HP ^{129}Xe imaging of the brain.

22.3.2 Polarizing ^{129}Xe and Required Hardware

Typically, ^{129}Xe is polarized using spin exchange optical pumping (SEOP). For high resolution ^{129}Xe brain imaging to be possible, the polarization level

should be initially high (40–50%) and persist until reaching its target organ such as the brain. The methods used to handle and administer the gas are key. After the gas is polarized and collected cryogenically, the gas is rapidly sublimated and trapped in a Tedlar[®] bag which is known for its favourable relaxation properties for HP gases. The size of bag or container also plays a role in relaxation and has been studied.⁴⁹ Many processes work to decrease polarization levels after production, such as the presence of paramagnetic oxygen, magnetic field gradients and the cryo-separation of xenon from buffer gases where improvements in cryo-trapping apparatus may help. It is important to note that any vessel used to contain HP ^{129}Xe should be impurity free, especially since oxygen can act to reduce T_1 to only minutes.

Producing and working with HP ^{129}Xe is non-trivial. In addition to the fundamental physics, many practical considerations must be made governing cost, hardware and experimental design. Xenon is a relatively inexpensive noble gas and is easily produced as a valuable by-product from fractional distillation of air in the liquid oxygen industry. In fact, air contains $0.087 \mu\text{L L}^{-1}$ of xenon.⁵⁰ Though extraction of xenon from air is an economical means of production, only 26% of the xenon extracted are those of the isotope ^{129}Xe . This natural abundance xenon can be purchased inexpensively in North America for about \$5–\$10 per L, though prices are on the rise. The cost rises dramatically to \$200–\$300 per L for purified versions of the gas with enrichment levels approaching 79–89% ^{129}Xe . In addition to the costs of consumables such as ^{129}Xe gas, medical grade buffer gases and gas administration apparatus (*e.g.*, tubes and Tedlar[®] bags), hardware and specially trained personnel required for producing HP ^{129}Xe can also be very expensive. A site interested in performing HP ^{129}Xe imaging of any sort will require a scanner equipped with a multi-nuclear hardware package and may require custom interface boxes and RF coils to perform imaging. With increased general interest in non-proton nuclei, this is becoming less of a problem (*e.g.*, ^{13}C metabolism studies, HP ^3He and ^{129}Xe lung imaging, ^{19}F lung imaging and cell tracking, and ^{23}Na brain imaging). There are a few commercial options available today for purchasing ^{129}Xe polarizers. Two prominent companies, Polarean Inc and Xemed LLC both offer ^{129}Xe polarizers capable of producing polarized gas and in clinical quantities (1–2 L per run). The Xemed system is capable of producing litre quantity gases at polarizations of up to 50%, levels which are desperately required for future studies of the brain using ^{129}Xe . There are also non-commercial and less expensive alternatives for HP ^{129}Xe production. There is an abundance of literature documenting the construction of several home-built systems,^{18,23,37,39,51–53} as well as an open-source batch-mode ^{129}Xe polarizer produced using 3D printing for rapid prototyping and reproducible deployment.¹⁷

22.3.3 ^{129}Xe Routes of Delivery for *In vivo* Applications

There are two ways to introduce ^{129}Xe into the body as a polarized gas contrast agent: (i) inhalation and (ii) injection. Using method (i) one must

consider development of a single breath breathing scheme or a multiple breath breathing scheme with the intention of saturating the blood with ^{129}Xe spins for delivery to the brain. A few drawbacks are immediately apparent for human consumption. Saturating the blood with enough ^{129}Xe for detection in the brain will depend on the content of ^{129}Xe within the inhaled breath, the duration of the breath-hold (or number of anoxic breaths) and the overall size of a batch of xenon achievable by the polarizer for a brain scan in a single batch. Furthermore, the ^{129}Xe that produces a dissolved phase signal in lung parenchyma and blood only represents 2% of the total inhaled xenon volume.²⁹ A limiting factor in achieving these conditions also arises from xenon's anaesthetic properties in alveolar concentrations greater than 70%^{54,55} (see Physiological Effects and Patient Safety below). Since the lung acts as a reservoir for ^{129}Xe exchange with blood, there is a trade-off between alveolar oxygen content, which reduces T_1 (for ^{129}Xe in the lung), and arterial oxygen content which lengthens T_1 (for dissolved ^{129}Xe in blood). An optimized gas mixture needs to be investigated enabling reasonable T_1 in lungs and long T_1 in blood. Peled *et al.* and Zhou *et al.* have laid the groundwork in determining xenon transit times and optimal oxygen/xenon mixtures that produces maximal rat brain signal based on model and experimental results.^{56,57} Kilian *et al.* later reported the first results demonstrating wash-in and wash-out effects of ^{129}Xe in the human brain.¹² Method (ii) involves the use of HP ^{129}Xe dissolved in a biocompatible solvent such as a lipid emulsion (Intralipid), perfluorooctyl bromide (PFOB) or saline. Benefits of this method include avoidance of inefficient delivery of ^{129}Xe from alveoli to capillary blood (due to the low partition coefficient for xenon in blood of about 0.17(5)), avoidance of depolarization of ^{129}Xe by oxygen in the alveolar spaces, lengthened T_1 compared to oxygenated blood, and requires much smaller quantities of ^{129}Xe per experiment. The first works in the development of an injectable ^{129}Xe contrast agent were performed by Bifone *et al.*, Goodson *et al.*, Wolber *et al.* and Venkatesh *et al.* using ^{129}Xe dissolved in a lipid emulsion (Intralipid 20%),^{43,58,59} PFOB,^{59,60} saline⁵⁹ and liposomes.⁵⁹ Important groundwork on the determination of ^{129}Xe diffusion coefficients in different solvents was also performed.⁶¹ Work with Intralipid 20% and 30% was continued by Duhamel *et al.*⁶² and Choquet *et al.*⁶³ where the chemical shift of ^{129}Xe dissolved in Intralipid was determined to be 194.5 ppm relative to gas, had T_1 relaxation values between 23 and 30 seconds at 2.35 T and was used to deliver ^{129}Xe to rat brain tissue where $T_{1,\text{tissue}}$ was measured to be 3.6 seconds.⁶³ PFOB targeted delivery methods were later studied for intratumoral investigations of ^{129}Xe exchange and relaxation within different types of tumours, the first tumour study of its kind.⁶⁴ Theoretical developments followed, regarding relationships to line broadening due to chemical exchange.^{65,66} A simpler approach was later tested by Driehuys *et al.* using saline as a solvent for ^{129}Xe .⁶⁷ They reported the highest intrasolvent T_1 for ^{129}Xe of 120 s at 2 T and injected the mixtures into the catheterized jugular vein or tail vein. Imaging was performed capturing HP ^{129}Xe that had crossed the blood-gas barrier and entered the

alveolar spaces from the blood. Though slightly more invasive than ^{129}Xe inhalation for delivery of contrast to organs, ^{129}Xe dissolved or mixed in solvents and injected for delivery to specific organs may be the best choice for delivery. Intralipid, PFOB and saline have been used and though ^{129}Xe dissolved in saline has a superior T_1 , the chemical shift of ^{129}Xe in saline may overlap and interfere with actual ^{129}Xe resonances in the brain. With a chemical shift of 100 ppm away from both tissue and gas resonances, PFOB may be the best choice and it possesses longer T_1 values compared to highly oxygenated blood as a carrier.

22.3.4 Physiological Effects and Patient Safety

Ultimately, in order to fully develop these techniques for translation to routine clinical use, patient safety must also be considered. Xenon is a known fast acting and potent anaesthetic in alveolar concentrations greater than 70%.^{54,55} ^{133}Xe , another isotope, though radioactive, also has a long known track record for safety^{68,69} and has also been used as an injected radiotracer.⁷⁰ Recent literature describe lung imaging with HP ^{129}Xe , describing a wide range of standards for administering inhaled HP ^{129}Xe from pre-determined alveolar concentrations (*e.g.*, 35%),⁷¹ mixtures of ^4He or N_2 with ^{129}Xe in 1 L total⁷² volumes to doses as high as 1 L of xenon in a single breath-hold independent of lung volume^{73,74} and as much as 2 L per visit.⁷⁵ Though some subjects reported minor transient effects such as dizziness, in all cases, no serious adverse events were reported. Despite subjects that are suffering from respiratory difficulty, such as those with chronic obstructive pulmonary disease (COPD), breath-hold studies using ^{129}Xe have been well tolerated for breath-hold durations up to 16 seconds.⁷⁶ In short, xenon has been used for a variety of applications over the last few decades for anaesthesia and imaging techniques (nuclear medicine and MRI) and has a proven safety track record.

Xenon administered in sub-anaesthetic concentrations has also been shown to demonstrate neuroprotective effects without neurotoxic properties⁷⁷ in models of hypoxic-ischemia in the brains of mice and rats.^{78,79} Xenon acts to reduce the release of neurotransmitters during a hypoxic-ischemia event, which is believed to play a key role that causes damage or death for nerve cells.⁷⁹ Dingley *et al.* showed that 3 hours of exposure to xenon after a 90 min ischemic insult provided neuroprotection, which may be translatable to treating human perinatal hypoxia-ischemia.⁸⁰ Localizing ^{129}Xe using MRI may elucidate brain regions benefitting from this treatment.

22.4 ^{129}Xe NMR and MRI of the Brain

Since the introduction of HP ^{129}Xe MR imaging,¹ research in animal and human brain imaging has been conducted. The first preliminary *in vivo* brain spectrum was reported by Mugler *et al.*¹⁰ and the signal dynamics from

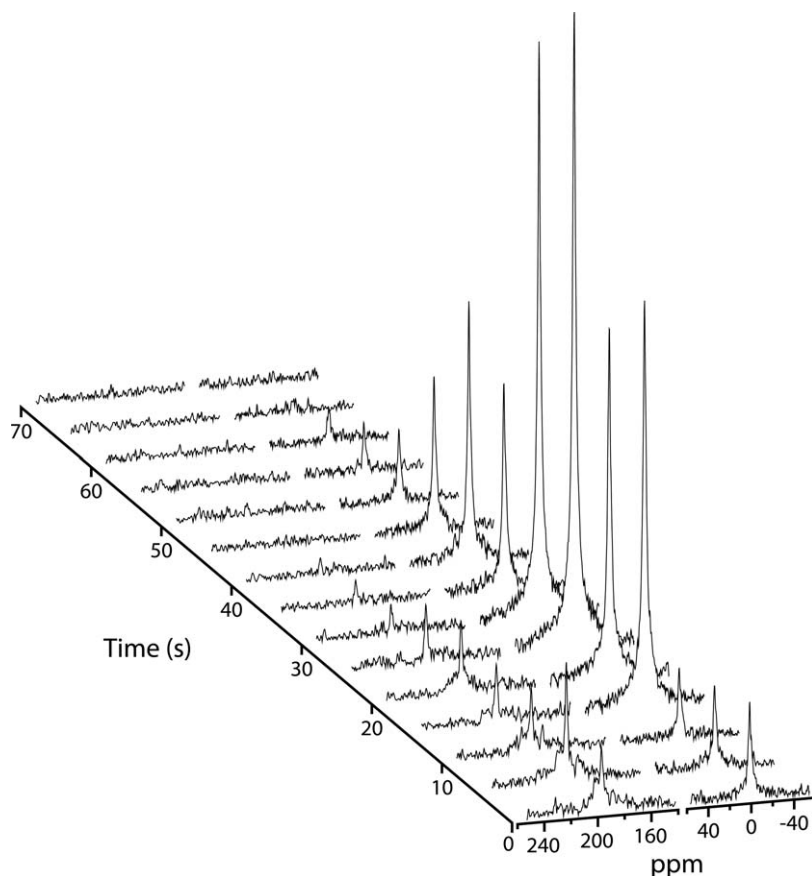


Figure 22.1 Fifteen consecutive ^{129}Xe spectra (one spectrum was acquired every 5 s) from the head of a healthy human volunteer. These data demonstrate the temporal evolution of the gas-phase and dissolved-phase signal components during and after a 15 s breath-hold period. Copyright © 1997 WileyLiss, Inc., A Wiley Company.¹⁰

spectra obtained from the human head were shown (Figure 22.1). The signal dynamics demonstrated the appearance of dissolved phase ^{129}Xe in the brain (196 ppm relative to gas) which were dynamically consistent with the lung-to-brain transit time of 4–5 seconds.^{10,56} At the same time, Swanson *et al.* investigated *in vivo* ^{129}Xe brain signals in animal models.¹¹ They performed both spectroscopy and chemical shift imaging and also observed dissolved phase ^{129}Xe localized to the brain at 194.5 ppm (Figure 22.2). Due to the difficulty of performing brain imaging with the low polarization that was available at the time ($\sim 2\text{--}3\%$), little progress in ^{129}Xe human brain imaging was made since these initial studies. Kilian *et al.* demonstrated the first 2D CSI map of ^{129}Xe distribution in the human brain using single breath techniques, which are more suitable and less invasive for humans

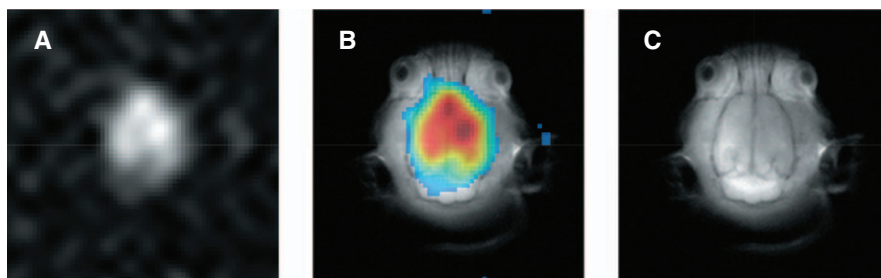


Figure 22.2 Coronal ^{129}Xe and ^1H images of the rat brain. (A) The ^{129}Xe rat brain image is shown with a maximum SNR of 20. (B) The false colour superposition the ^{129}Xe and ^1H images, demonstrates that the ^{129}Xe signal arises entirely from within the brain as well as reduced ^{129}Xe in the cerebellum. (C) ^1H spin-echo image. Copyright © 1997 WileyLiss, Inc., A Wiley Company.¹¹

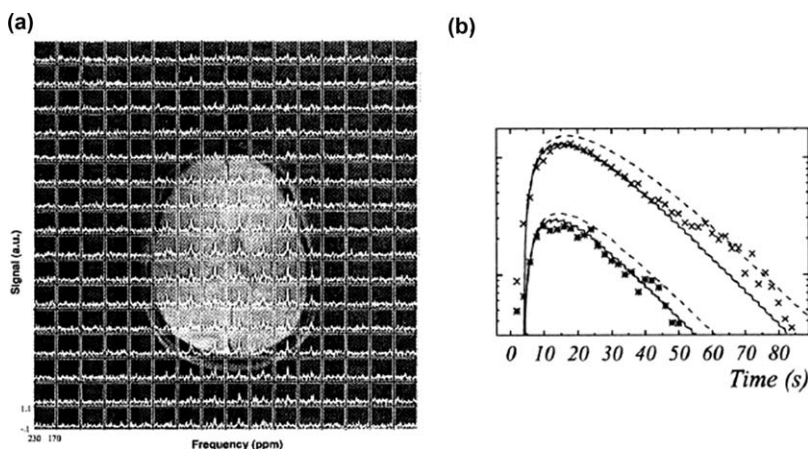


Figure 22.3 (a) ^{129}Xe CSI superimposed onto a ^1H image demonstrates the presence of hyperpolarized ^{129}Xe dissolved in brain tissue in this healthy human volunteer. (b) Time-resolved dynamics of scaled amplitudes of the 196.5 ppm and 193 ppm spectral lines. These data were fitted to a theoretical model describing ^{129}Xe transit to the brain. Copyright © 2004 WileyLiss, Inc.^{12,81}

than methods used in previous animal studies⁸¹ (Figure 22.3a). Later, Kilian proposed a theoretical model to describe xenon transit to the brain and showed that the longitudinal relaxation rates in grey and white matter were significantly different, with grey matter having the longer of the two¹² (Figure 22.3b). The latter study reports the highest ever reported breath-hold duration for ^{129}Xe at about 40 s. These studies laid the groundwork for future development of ^{129}Xe brain imaging with the potential to measure both cerebral blood flow (CBF) and even brain function (in an analogous way to BOLD techniques).

Animal work continued after the experiments of Mugler *et al.* and Swanson *et al.* in order to better understand the observed dissolved phase spectra in the brain. The previously obtained peaks were broad, the field strengths were low (1.5–2 T) and the achievable levels of polarization were also low (about 2%). Wakai *et al.* made progress in an animal model that used continuous breathing of a ^{129}Xe gas mixture and extensive averaging in the head region, and multiple peaks were identified over a large range of chemical shifts (185–210 ppm)⁸² (Figure 22.4). It was previously believed that the peak at 196 ppm was that of tissue and blood; however, in this spectrum, a peak at 210 ppm was resolved and was consistent with blood peaks measured in the chest regions and was hence reassigned. Therefore, the peak at 196 ppm was assigned to “tissue only”, with the other two peaks in the spectrum remaining unknown. At the same time, Kimura *et al.* made improvements to measuring *in vivo* T_1 of ^{129}Xe in the mouse brain and reported a value of 14.1 seconds.⁸³ Kershaw *et al.* later set out to identify the remaining unidentified peaks and their apparent inconsistencies in the literature and devised an experiment to answer these questions. They definitively found through the use of an animal model involving external carotid artery and pterygopalatine artery ligation, that two peaks belonged

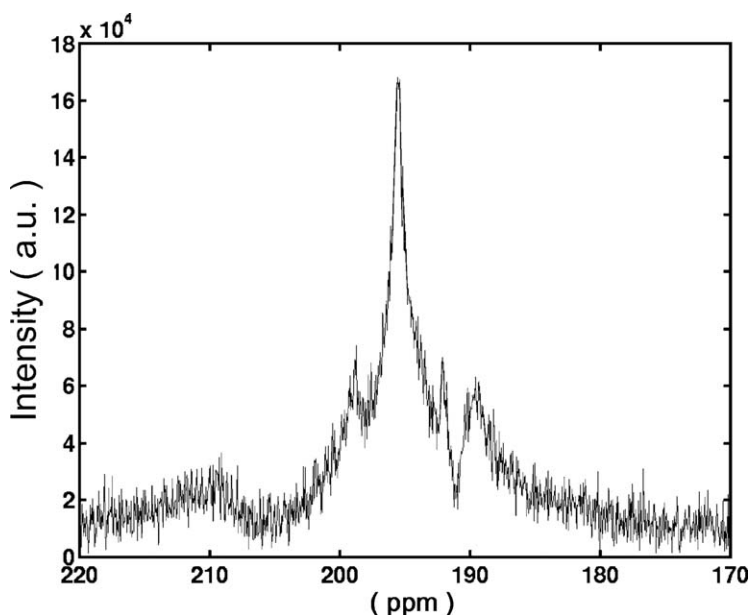


Figure 22.4 NMR spectroscopy of ^{129}Xe in the rat head. A representative spectrum was obtained by averaging 60 times. Wakai *et al.* determined that the peaks at 210 and 196 ppm relative to the gas phase peak might correspond to ^{129}Xe in blood and brain tissue, respectively. Reprinted from ref. 82, Copyright (2004), with permission from Elsevier.⁸²

to brain tissue and assigned them grey (193–197 ppm) and white matter (191–194 ppm) which was confirmed by the disappearance of the other peaks post ligation⁸⁴ (Figure 22.5). They also demonstrated that the inconsistencies in the other peaks were not due to shim or anaesthetic effects. Zhou *et al.* revisited the problem of T_1 relaxation measurements in the brain and determined experimentally in animal models that noise considerations are crucial for computing reliable brain T_1 relaxation times *in vivo*.⁸⁵ Nouis *et al.* recently reported on a significant advancement compared to previously reported imaging methods in animals (described below) offering faster and higher resolution 3D images with isotropic voxels using a 3D radial acquisition method (Figure 22.6).⁸⁶ This imaging technique offers fast scan times and high SNR compared to much slower CSI techniques reported by Mazzanti *et al.*¹⁴

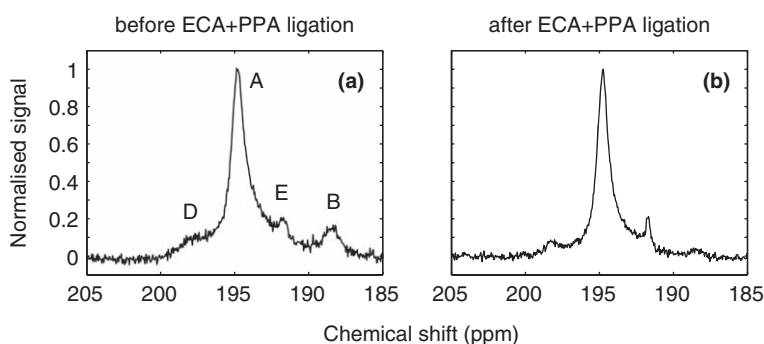


Figure 22.5 Examples of ^{129}Xe dissolved phase spectra obtained within the same rat (a) before and (b) after ligation of the external carotid artery (ECA) and pterygopalatine artery (PPA). Peaks B and D are clearly diminished after ligation while peaks A and E remain. Copyright © 2007 WileyLiss, Inc.⁸⁴

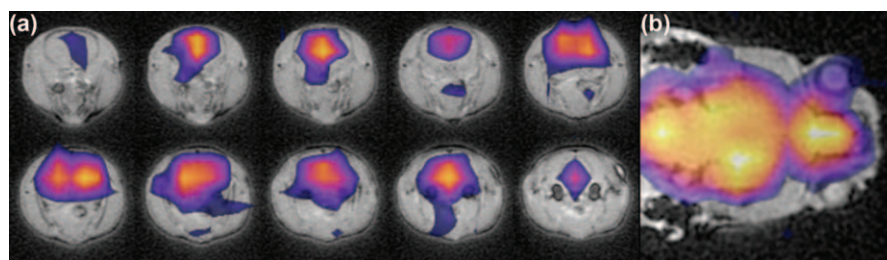


Figure 22.6 (a) Axial and (b) coronal 3D images, with isotropic resolution, of distribution of ^{129}Xe in the rat brain. The dissolved HP ^{129}Xe signal (color) is overlaid on a ^1H anatomical image (grayscale), and the ^{129}Xe signal qualitatively matches the brain tissue. Images courtesy of Bastiaan Driehuys.

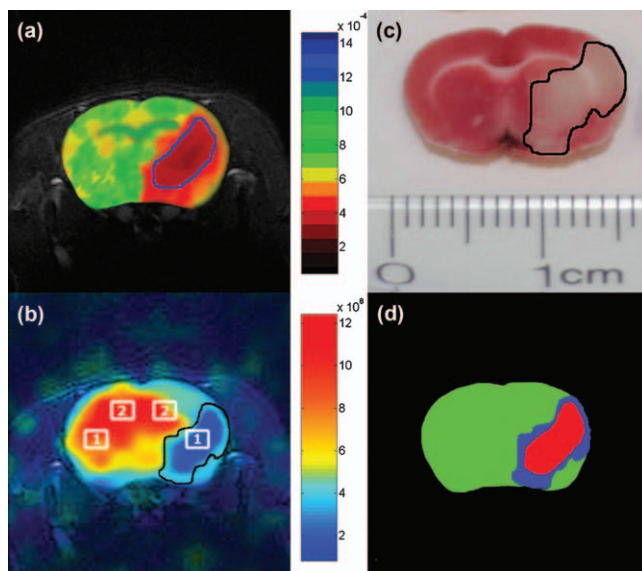


Figure 22.7 ^1H and ^{129}Xe imaging of a model of ischemic stroke in the rat brain. (a) ^1H diffusion weighted imaging indicating a region of poor perfusion (ischemic core). (b) Corresponding ^{129}Xe CSI map depicting signal void in the region of the ischemic core. (c) Histological confirmation of stroke model related ischemia. (d) Tri-colour map depicting normal tissue (green), ischemic core (red) and penumbra (blue). Copyright © 2010 John Wiley & Sons, Ltd.¹³

Zhou *et al.* and Mazzanti *et al.*, published the first results using ^{129}Xe brain imaging techniques for measurement of cerebral ischemia (stroke model) and cortical brain function in animals respectively. Using a stroke model (middle cerebral artery occlusion) Zhou *et al.* showed that ^{129}Xe manifests as observed signal voids in regions of the ischemic core, verified by diffusion weighted imaging and histology (Figure 22.7).¹³ Similarly, Mazzanti *et al.* measured cortical brain function using ^{129}Xe CSI (Figure 22.8). Maps were measured at baseline and post-stimulus. The stimulus was a small injection of capsaicin into the forepaw of the animal to evoke a pain response. Increased ^{129}Xe signal and signal difference maps in regions of the brain responsible for processing pain response were observed compared to baseline.¹⁴ The latest reported ^{129}Xe mouse brain literature is by Imai *et al.* They developed a fast method for quantitative measurements of ^{129}Xe signal dynamics by repeated application of RF pulses after a steady state ^{129}Xe concentration has been reached using carefully controlled ventilation schemes.⁴⁸ Their methods incorporate dynamic changes due to cerebral blood flow, partition coefficient for blood and tissue and T_1 relaxation. These measurements have applications to mouse models of brain function such as kainic acid induced epilepsy.

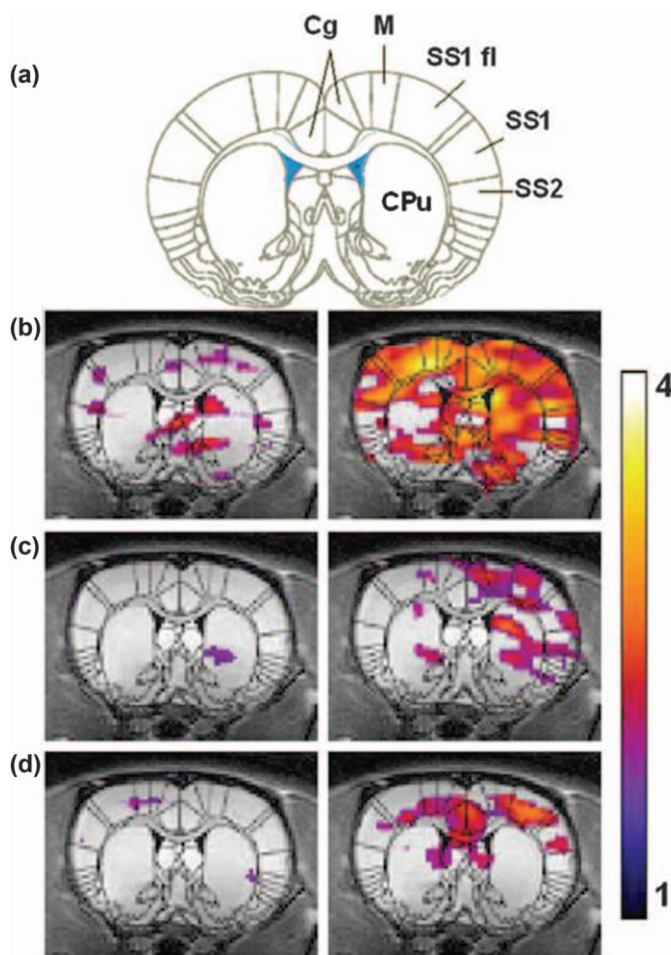


Figure 22.8 ^1H and ^{129}Xe imaging of a model of pain response in the rat brain. (a) Rat brain atlas indicating several important brain regions such as the cingulate cortex (Cg), primary somatosensory cortex (SS1) and secondary somatosensory cortex (SS2). (b)–(d) depict rat brain CSI maps registered to their corresponding ^1H brain images. The left column shows data obtained at baseline and the right column are maps obtained post injection of capsaicin. Each set of maps taken in (b) through (d) are obtained within the same animal, hence $n = 3$.
© 2011 Mazzanti *et al.*¹⁴

22.5 Conclusions

It is clear that substantial ground-work and refinements have been achieved in this field, from gas production, acquisition methods, delivery methods, theoretical models and animal models. To make brain imaging possible, transition from lower field strengths (1.5–2 T) to higher fields (3–4.7 T) helped bring about enough spectral resolution to allow for the identification

of several dissolved phase peaks identifying blood, grey and white matter. ^{129}Xe relaxation in blood has also been investigated in detail and is now better understood. Enhancements in xenon polarizer technology and the increase in commercial and non-commercial options have greatly improved the polarization levels achievable and availability of HP ^{129}Xe , which has had dramatic improvement in image SNR. The use of enriched ^{129}Xe mixtures also serves to easily improve SNR by a factor of 2–3 times at higher cost per litre of gas, but combined with injection methods, and due to the low volumes consumed may be more effective and economical. Now, with enriched ^{129}Xe polarized to levels of 40–50% and in litre quantities, single breath-hold brain imaging may also be possible, perhaps allowing for *in vivo* investigations of Alzheimer's disease, stroke and fMRI in humans.

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CHAPTER 23

Beyond Spin $I = 1/2$; Hyperpolarized ^{131}Xe and ^{83}Kr Magnetic Resonance

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23.1 Overview

The large chemical shift range of ^{129}Xe is the basis of many of the captivating studies described in the various chapters of this book. The only other stable noble gas isotope with nuclear spin $I=1/2$, ^3He , lacks any appreciable chemical shift range. Beyond spin $I=1/2$, there are two stable noble gas isotopes, ^{83}Kr ($I=9/2$) and ^{131}Xe ($I=3/2$), that occur at sufficiently high natural abundance for practical applications. Unfortunately the usable chemical shift ranges associated with these isotopes are inferior to that of ^{129}Xe . However, spin $I>1/2$ isotopes have a nuclear electric quadrupole moment that enables a host of supplementary magnetic resonance studies. The spin $I>1/2$ noble gas isotopes can all be hyperpolarized but their ‘quadrupolar’ relaxation times are fairly short causing rapid depolarization compared to hp ^{129}Xe . This chapter reviews how this apparent disadvantage can be turned into a useful probe for surfaces in material sciences and biomedical research. This unique probe can ‘sense’ surfaces at far lower

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

surface to volume ratios (S/V) than the ^{129}Xe chemical shift. The underlying physical concept will be illustrated in the first part of the chapter using the 'simpler' $I = 3/2$ isotope ^{131}Xe that has 4 Zeeman energy levels rather than the 10 levels of ^{83}Kr . The second part will focus on use of ^{83}Kr that strikes the best balance between achievable signal intensity and utility for novel, surface indicative MRI contrast.

23.2 ^{131}Xe NMR and MRI

23.2.1 The Energy Levels of the Spin $I = 3/2$ Isotope ^{131}Xe

The four Zeeman energy levels of ^{131}Xe , depicted with the corresponding spin states in Figure 23.1a, show equal energy level separation. The selection rule $\Delta m_z = \pm 1$ leads to three allowed transitions with identical resonance frequency resulting in a single peak in the NMR spectrum. At this level of description, there is little apparent difference to that of a gas phase ^{129}Xe NMR singlet. Note that the chemical shift behaviour of the two isotopes is the same in relative (ppm) units but, because of the lower resonance frequency of ^{131}Xe (see Table 3.1 in Chapter 3), the range in absolute units (Hz) is approximately 3.4 times less than that of ^{129}Xe . However, as for

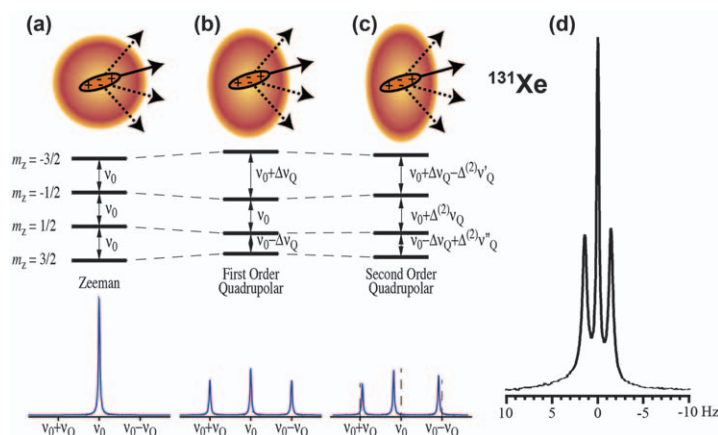


Figure 23.1 ^{131}Xe Zeeman energy level diagram (nuclear spin $I = 3/2$; nuclear electric quadrupole moment) and the resulting spectra, illustrating the effect of nuclear quadrupolar interaction with an electric field gradient (EFG) caused by the distortion of the xenon electron cloud. (a) Spherical symmetry (no distortion) and therefore no EFG present resulting in a (simulated) spectrum with no splitting present. (b) Weak distortion, causing a first order quadrupolar coupling and therefore a symmetric triplet in the simulated spectrum. (c) Severe distortion of the electron cloud leads to a second order coupling and thus an asymmetric splitting in the associated spectrum. (d) Actual hp ^{131}Xe gas phase NMR spectrum at 11.75 T displaying the quadrupolar triplet, from work by Stupic *et al.*¹⁷ (d) Copyright 2011 Elsevier; under a Creative Common License.

any $I > 1/2$ nuclear spin, the nuclear charge distribution is non-spherical resulting in a nuclear electric quadrupolar moment. The presence of an electric field gradient (EFG) is required for nuclear electric quadrupole interactions to occur. Electric quadrupolar interactions are of short range but 'local' EFG's can be generated by the surrounding electron cloud provided that a non-spherical electron distribution is present. In molecules, quadrupolar interactions are usually in the order of many MHz but spherical electron distribution in a single atomic system such as xenon does *not* cause EFGs. However, electrostatic interactions of the xenon atom with the molecular environment can lead to a distortion of the electron cloud, breaking the spherical symmetry, and the resulting EFG causes a shift in the energy levels, as shown in Figure 23.1b. To a first order approximation, the center transition is not affected but the satellite transitions will appear at higher and lower frequencies. The effect is dependent on the extent of the electron cloud distortion but also on its orientation with respect to the magnetic field B_0 . In an oriented medium, such as a liquid crystalline phase, the resulting net energy level shift leads to a triplet in the ^{131}Xe NMR spectrum and to nine observable lines for ^{83}Kr , as shown by Jokissari and co-workers.^{1,2}

In randomly oriented porous solids, a powder-pattern type of spectrum can be observed for ^{131}Xe , as shown by Ripmeester, Moudrakovski, and co-workers.³ Furthermore, severe distortions of the electron cloud, as sketched in Figure 23.1c, can lead to second order effects and hence to a shift in the centre transition³ (see also work by Fraissard and co-workers^{4,5}). Quadrupolar interactions have been observed with thermally polarized ^{131}Xe in the dissolved phase, in nano-porous media, or even with molecules⁶ and are typically very large (*i.e.* kHz to MHz). Unfortunately, application of hyperpolarized (hp) ^{131}Xe to these systems is not practical due to fast quadrupolar T_1 relaxation times of a few tens of milliseconds or less. The following two sections describe the hp ^{131}Xe NMR observed in the gas phase where the T_1 times can be on the order of many seconds.

23.2.2 Hyperpolarized ^{131}Xe and Gas Phase ^{131}Xe T_1 Relaxation

Gaseous ^{131}Xe can be hyperpolarized through alkali metal vapor spin exchange optical pumping (SEOP) as explored by Volk,^{7,8} Happer,^{9–13} Pines,¹⁴ Mehring,¹⁵ Luo¹⁶ and their respective co-workers. The studies with hp ^{131}Xe were typically conducted in the presence of alkali metal vapor using optically detected NMR experiments. Similar to SEOP with ^{83}Kr described in Chapter 3, our group has successfully separated the rubidium vapor from hp ^{131}Xe after SEOP and subsequently transferred the gas into superconducting magnets, thus making it available for high field NMR and MRI experiments.¹⁷ The spectrum displayed in Figure 23.1d was observed at 11.75 MHz after Rb removal and transfer of hp ^{131}Xe into a pre-evacuated NMR detection cell.

As described in Chapter 3, high xenon or krypton densities adversely affect ^{129}Xe and ^{83}Kr SEOP. This is also true for ^{131}Xe SEOP but there is an additional effect that further exacerbates the situation, namely the fast, xenon density dependent, gas phase T_1 relaxation that was quantified in earlier work by Brinkmann and co-workers¹⁸ with:

$$1/T_1^{^{131}\text{Xe}} = \rho \cdot 3.95 \times 10^{-2} \text{ amagat}^{-1} \text{ s}^{-1}. \quad (23.1)$$

Note that this equation only describes the contribution arising from binary Xe–Xe gas phase collisions. At a xenon density ρ of a few amagat and beyond, the binary collisions become the dominant contribution to relaxation (see Chapter 3 for a definition of the amagat). At ambient pressure and temperature (*i.e.* at a Xe density of approximately 1 amagat) eqn (23.1) predicts a ^{131}Xe gas-phase relaxation time of $T_1^{^{131}\text{Xe}} \approx 25$ s for pure xenon gas. However, the formation of Xe– ^{131}Xe van der Waals complexes leads to an additional relaxation term¹⁹ that is gas density independent at lower magnetic field strengths. In addition, collisions with the surface will further reduce the longitudinal relaxation time. These contributions to the resulting ^{131}Xe gas phase relaxation are reminiscent of those affecting the ^{129}Xe gas phase relaxation, as discussed by Saam²⁰ in Chapter 7. However the dominating relaxation mechanism for the spin $I = 3/2$ isotope is based on quadrupolar interactions rather than on spin-rotation, dipolar, or chemical shift anisotropy effects. The schematics in Figure 23.2 depicts mechanisms

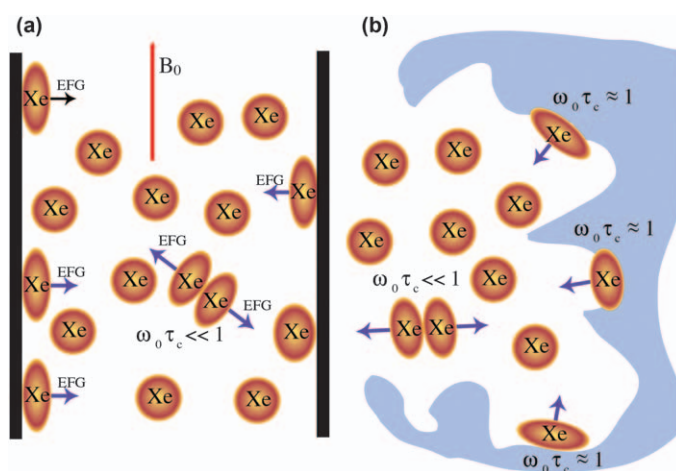


Figure 23.2 Sketch of xenon gas phase collisions and surface adsorption events (likewise valid for krypton). (a) In a plain glass container where surface adsorption and subsequent exchange will cause a net splitting observed in the gas phase; (b) on the high surface of a porous medium with random orientation that does not produce any observable net quadrupolar coupling in the gas phase. Surface relaxation is always present and contributes, through exchange, to the relaxation measured in the gas phase. Arrows indicate EFG tensor orientation.

of collisions and surface adsorption that cause distortions of the Xe electron cloud. These events generate EFG's with short life-times and thus results in fluctuating quadrupolar interactions. Fast averaging from many events (with random orientation) prevent a quadrupolar spitting. However, the associated fluctuation in the energy levels will have correlation times that are determined by the duration of the collisions and adsorption events. As a consequence, fast quadrupolar relaxation occurs that is almost always the dominating relaxation mechanism for ^{131}Xe .

Three different Xe concentrations were used for ^{131}Xe SEOP in ref. 17, and the highest spin polarization with $P=2.2\%$ was obtained with 5% Xe: 5% N_2 : 90% He. A 40 W diode array laser was applied without line narrowing to the SEOP mixture at 150 kPa (1.5 bar) pressure and 453 K. The polarization was reduced to $P=0.44\%$ for the 20% Xe: 5% N_2 : 75% He gas mixture and a very low $P=0.026\%$ resulted when 93% Xe: 7% N_2 was used. It was concluded that SEOP with ^{131}Xe is far more adversely affected by high xenon densities than ^{129}Xe SEOP (or ^{83}Kr SEOP by high krypton densities). This behavior is a consequence of the density dependent relaxation described in eqn (23.1), and the apparent polarization P_{app} , defined in eqn (3.9), is very low for all mixtures used. Its 'highest' value of $P_{\text{app}}=0.13$ is obtained with the 20% Xe mixture. Strikingly, this value is only marginally larger than $P_{\text{app}}=0.11$ obtained with the 5% Xe mixture. Taking into account relaxation during $\text{hp } ^{131}\text{Xe}$ transfer, the highest $\text{hp } ^{131}\text{Xe}$ MR signal intensity can be expected with this most dilute xenon. As in the case of ^{83}Kr SEOP, higher laser power and laser narrowing may significantly improve the achievable polarization P and apparent polarization P_{app} .

23.2.3 The Origin of Gas Phase Quadrupolar Splittings – The Surface Effect

In early SEOP studies, a small splitting (<1 Hz) of the (optically) detected magnetic resonance signal of $\text{hp } ^{131}\text{Xe}$ was observed within cylindrical SEOP cells.^{8–11,14,15,21} This splitting was found to be strongly dependent on the orientation of the axis of the cell with respect to the magnetic field and on the aspect ratio of the centimetre-sized cylinder. Remarkably, the splitting was not observable in spherical SEOP cells. Mehring and co-workers also observed $\text{hp } ^{83}\text{Kr}$ quadrupolar splitting in cylindrical SEOP cells²² and applied a rotating glass cell to construct a geometric quantum-phase based gyroscope that utilized the $\text{hp } ^{131}\text{Xe}$ quadrupolar splitting^{23–25} (see also ref. 26 and 27).

The sketch in Figure 23.2a visualizes how a gas phase splitting can originate from the surrounding surface. The xenon atoms at the container wall will experience a distortion and therefore an EFG for the short time of the adsorption event. Mehring and co-workers have determined a resulting ^{131}Xe quadrupolar coupling of 6.17 MHz on the Duran glass surface at the conditions of their experiment.^{15,21,22} The large coupling will however only result in a small phase evolution of the transverse ^{131}Xe magnetization

because of the brief duration of adsorption, typically on the nanosecond time scale. However, repeat adsorption will lead to a continuation of the phase evolution, provided that the orientation of the Xe-surface adsorption with respect to the magnetic field remains constant. This is the case for the surface of a cylindrical cell when its axis is aligned with the magnetic field lines and the sum of many short adsorption events will cause a slow phase evolution. As a result, a small quadrupolar coupling is observable in the ^{131}Xe gas phase NMR spectrum. The coupling is scaled by the ratio of the time that the xenon atoms are on the surface to the (much larger) time that they spend in the gas phase. Quadrupolar couplings from randomly oriented EFG's during gas phase collisions are averaged to a zero phase evolution and are therefore not contributing to the splitting (a similar argument can be made for $\text{Xe}-^{131}\text{Xe}$ van der Waals dimers). These events do however cause quadrupolar relaxation as discussed in Section 23.2.2. Remarkably, the net phase evolution will also be zero in a spherical cell provided the gas diffusion is large enough to allow for the xenon atoms to sample all surface orientations. In this case, no ^{131}Xe splitting will be observable due to orientational averaging. The schematics in Figure 23.2a are somewhat naïve as they depict the surface without the corrugation that is present in glass surfaces. Although the modulation of the surface may reduce the quadrupolar splitting to some degree through orientational averaging, it will not prevent the splitting completely as long as a net surface orientation with respect to the magnetic field is present. Figure 23.2b sketches a randomly oriented surface where the net quadrupolar coupling will likely be averaged out to zero. However, even if the net coupling is averaged to zero and no splitting will be observed, the surface adsorption will always contribute to the ^{131}Xe relaxation measured in the gas phase.

A gas phase ^{131}Xe triplet can also be observed with radio frequency detected NMR spectroscopy at high magnetic fields. Figure 23.1d shows an hp ^{131}Xe NMR spectrum at 11.75 T with the gas located inside a 6 mm (inner diameter) NMR sample tube. However, the observed splitting is larger than expected from previous work at very low magnetic field strength. For better illustration of the effect, a number of (thermally polarized) ^{131}Xe spectra are shown in Figure 23.3. Remarkably, the magnitude of the quadrupolar splitting $2\nu_Q$ is dependent on the magnetic field strengths. This was unexpected as small (first order) quadrupolar interactions are magnetic field independent, but at high magnetic field strengths an additional effect is present that contributes to the observed splitting in the gas phase, as will be explained in Section 23.2.4.

Focusing the discussion on the surface effect for the moment, Figure 23.3 also shows the effect of the surface to volume ratio, S/V , upon the observed ^{131}Xe gas phase quadrupolar splitting. As S/V is increased without changing the net surface orientation (*i.e.* by adding glass capillaries), the quadrupolar splitting increases, independent of the magnetic field strength, by $\Delta(2\nu_Q) \approx 1.5$ Hz. With increasing S/V the ratio of surface adsorbed ^{131}Xe to

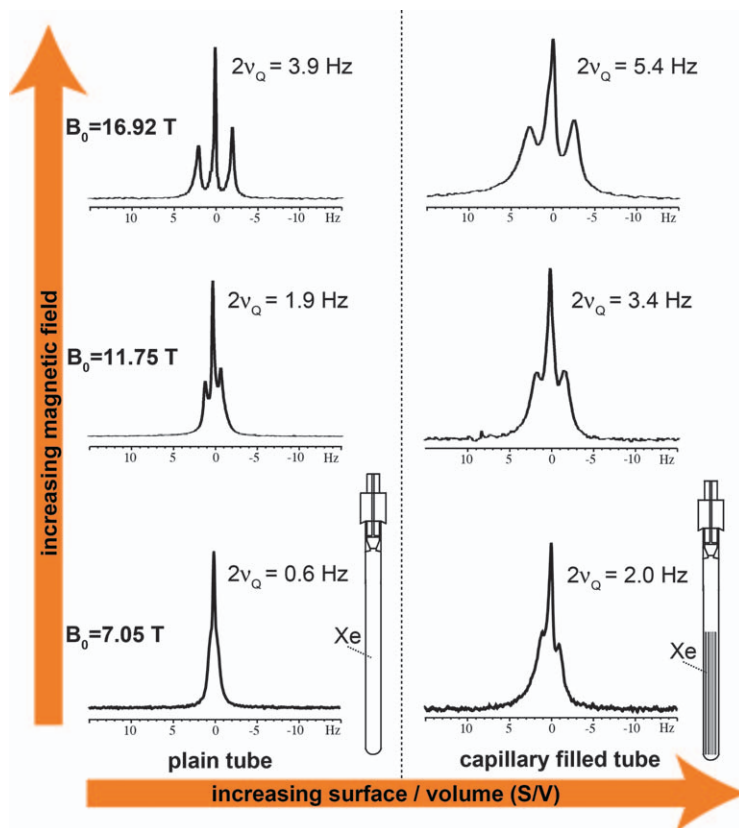


Figure 23.3 Thermally polarized ^{131}Xe gas phase NMR spectra at various field strengths at 400 kPa (4 bar) pressure of pure xenon gas. The resulting quadrupolar splitting is indicated as $2\nu_Q$. Left side: xenon gas is located in plain 6 mm inner diameter NMR tube. Right side: tube contains glass capillaries in an otherwise identical NMR tube and at the same xenon pressure.

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gas phase ^{131}Xe will increase and a larger splitting will occur in the gas phase.

There are other parameters that will affect the observed splitting. For example, with increased temperature, a decrease of the fraction of surface adsorbed xenon atoms will result in a reduced splitting. Most intriguingly, competitive co-adsorption of other molecules can result in a reduction of the splitting. The hp ^{131}Xe quadrupolar gas phase splitting in a macroscopic NMR tube was reduced by $\Delta(2\nu_Q) = 0.78$ Hz in the presence of water vapor.¹⁷ This effect demonstrates how little S/V is needed to observe surface effects through ^{131}Xe NMR. Note that many orders of magnitude larger S/V are required to affect the chemical shift of ^{129}Xe . For some samples, the ^{131}Xe

quadrupolar splitting will not be resolved due to line broadening that may arise, for example, from a magnetic susceptibility distribution throughout the sample. In this case, the quadrupolar coupling can still be monitored through multiple quantum filtered (MQF) experiments.^{28–30}

23.2.4 The Origin of Gas Phase Quadrupolar Splittings – The Magnetic Field Effect

A striking observation in Figure 23.3 is the magnetic field B_0 dependence of the ^{131}Xe quadrupolar splitting ($2\nu_Q$) that appears to follow approximately $2\nu_Q \propto B_0^2$.²⁹ The small quadrupolar splitting due to xenon–surface interactions, discussed in the previous section, is not expected to be affected by high magnetic fields. Furthermore, the difference in ^{131}Xe splitting $\Delta(2\nu_Q) \approx 1.5$ Hz between the plain tube and the capillary filled tube samples, an effect that was clearly caused by the surface, is independent of the magnetic field. In further experiments, not shown here, interaction of the (bulk) ^{131}Xe with the surface was largely suppressed using liquefied xenon.²⁹ Although the splitting was masked by the line broadening, multiple quantum filtered (MQF) measurements revealed that the removal of an effective surface only slightly reduced the splitting compared to the gas phase measurement in the plain tube. However, the magnetic field dependence, $2\nu_Q \propto B_0^2$, was found to be still valid. All these observations indicate that here are two effects: (1) a surface based effect and (2) an additional, different effect associated with high magnetic fields.

The origin of the high field effect, confirmed by subsequent theoretical work and further observation,^{31–33} is the distortion of the xenon electron cloud in the presence of a magnetic field. In a simple physical picture, when an atom or molecule is placed into a magnetic field $\vec{B}_0$, a ring current is induced causing a magnetic moment $\vec{M}$ that is opposed to $\vec{B}_0$. Of course, this is well known as the origin of chemical shift in NMR because the induced magnetic moment $\vec{M}$ reduces the magnetic field $\vec{B}_0$ experienced by the nucleus. However, interaction of $\vec{M}$ with $\vec{B}_0$ will result in an electron cloud deformation and the reduced symmetry leads to the generation of a small EFG. Electron cloud deformation happens with every substance that is placed into a high magnetic field but the effect is too small to cause an NMR observable effect at the magnetic field strengths currently available. The only exception, thus far, is ^{131}Xe and its nuclear quadrupole moment that sufficiently interacts with the weak EFG to cause an observable splitting. The observed B_0^2 dependence comes from the fact that the external magnetic field $\vec{B}_0$ will (a) first induce the magnetic moment $\vec{M}$ and (b) also interact with $\vec{M}$. It is observable because of the high sensitivity of the ^{131}Xe isotope to small electron cloud distortions and because of the narrow ^{131}Xe NMR line width found in the gas phase. Note the effect was not observable with ^{83}Kr at the magnetic field strengths applied in Figure 23.3.

23.2.5 ^{131}Xe MRI Contrast Using Quadrupolar Relaxation

Any interaction of ^{131}Xe with a surface will cause a relaxation effect that will contribute to the overall relaxation. Like the quadrupolar splitting, the effect is expected to scale with the surface to volume ratio S/V . Unfortunately, the ^{131}Xe T_1 relaxation in microporous materials ranges typically from milliseconds to tens of milliseconds and is therefore too short for practical hyperpolarized gas usage. However, rapid signal averaging makes thermally polarized ^{131}Xe NMR, and even ^{131}Xe MRI possible, provided the xenon density is sufficiently high. The first ^{131}Xe MRI experiments have utilized liquefied xenon in special single crystal sapphire tubes at high pressure and below the xenon critical temperature of 289 K. MRI contrast was generated through transverse (T_2) relaxation that originated on the surface of meso-porous aerogels and the contrast enabled distinction between various aerogel densities, an effect that was likely induced by the differences in S/V .³⁴ Furthermore, the contrast was also indicative of the (reversible) aerogel surface hydration. Surface hydration was further studied using ^{131}Xe multiple quantum filtered (MQF) NMR spectroscopy to distinguish between relaxation and coherent quadrupolar coupling as a function of aerogel hydration.³⁰ The presence of a coherent term suggested some form of order in the porous structure and this finding was supported by optical polarization microscopy. In summary, all these methods have in common that quadrupolar interaction on the surface is transferred through exchange into the bulk fluid phase (gas or liquid) where it is NMR or MRI detected. Surface quadrupolar interactions can cause both coherent evolution (*i.e.* splitting) or relaxation that is observable in the fluid phase.

23.3 ^{83}Kr NMR and MRI

The novelty of ^{131}Xe MRI, discussed in the previous sections, is that its contrast can be attributed to quadrupolar interaction on surfaces that surround the gas or liquid phase. The noble gas isotope ^{131}Xe is a particularly sensitive probe for surfaces because of its nuclear electric quadrupole moment and its very large electron cloud that is easily affected by electrostatic interactions. The major drawback of ^{131}Xe is that it is often a far too sensitive probe, causing very rapid relaxation. This makes hyperpolarized ^{131}Xe MRI impractical for most biomedical applications. What is therefore needed, is a similar but slower relaxing probe that allows for hyperpolarized gas application and still provides information of the surrounding surfaces. It just happens, that ^{83}Kr has exactly the right properties – a reduced but still very active quadrupolar nature due to its smaller electron cloud and because of its higher nuclear spin $I=9/2$. The detection of quadrupolar coupling in the gas phase with this isotope has been elusive thus far, but the ^{83}Kr longitudinal (T_1) surface quadrupolar relaxation (SQUARE) can be used as a novel probe for surfaces.

23.3.1 ^{83}Kr Gas Phase Relaxation – Good News for Biomedical MRI

The difference in the magnitude of the ^{83}Kr quadrupolar relaxation, as compared to ^{131}Xe , becomes immediately apparent when looking at the contribution of binary collisions to the gas phase relaxation. The krypton density ρ dependent part of the gas phase relaxation at a temperature of 298 K for pure krypton gas is:³⁵

$$1/T_1^{83\text{Kr}} = \rho \cdot 1.6 \times 10^{-3} \text{ amagat}^{-1} \text{ s}^{-1}, \quad (23.2)$$

making the ^{83}Kr relaxation about 25 times slower than the ^{131}Xe relaxation rate in eqn (23.1). At ambient pressure and temperature one can therefore expect a T_1 of about 10 minutes if only binary collisions would cause the spin relaxation. In analogy to the relaxation of the two xenon isotopes there is an additional, krypton density independent, contribution through the formation of ^{83}Kr – Kr van der Waals dimers.³⁶ The container wall will further shorten the T_1 , an effect that will depend on S/V , temperature, and magnetic field strength as explored previously through remotely detected relaxometry.³⁷

For practical intents and purposes, the following relaxation times may be of interest: using a 95% Kr : 5% N_2 mixture stored at a pressure of 120 kPa (1.2 bar) within a 1.25 cm inner diameter and 10 cm long Pyrex container at ambient temperature (297 K) and a magnetic field strength of 500 Gauss (0.05 T), the longitudinal relaxation was found to be $T_1 = 85$ s. The surface relaxation was most likely the dominant contribution to the gas phase relaxation in the small container. However, the surface contribution can be decreased by increasing the temperature and at 433 K a relaxation time of $T_1 = 220$ s was measured. It is probable that a larger container will similarly increase the T_1 times due to the reduced S/V . These relaxation times are quite short compared to those of ^{129}Xe but, in contrast to the fast relaxation of ^{131}Xe , they are still adequate to make biomedical usage of hp ^{83}Kr feasible. Furthermore, paramagnetic O_2 does not substantially shorten the ^{83}Kr T_1 times.³⁸

23.3.2 Exploring Model Surfaces with the Nuclear Spin $I = 9/2$ Isotope ^{83}Kr

Gas phase relaxation of ^{83}Kr may be adequate for practical MRI experiments – but only new and meaningful MRI contrast would justify the considerable effort required for ^{83}Kr SEOP and hp ^{83}Kr handling. To explore the potential value of surface sensitive hp ^{83}Kr contrast, a simple model surface was produced,³⁹ as shown in the schematics of Figure 23.4.

The model surface is made of (approximately) uniform glass beads that are placed in a 10.8 mm inner diameter sample tube. Various sizes of the glass beads (*i.e.* 0.1, 0.5, 1.0, and 2.5 mm diameter) were used to produce

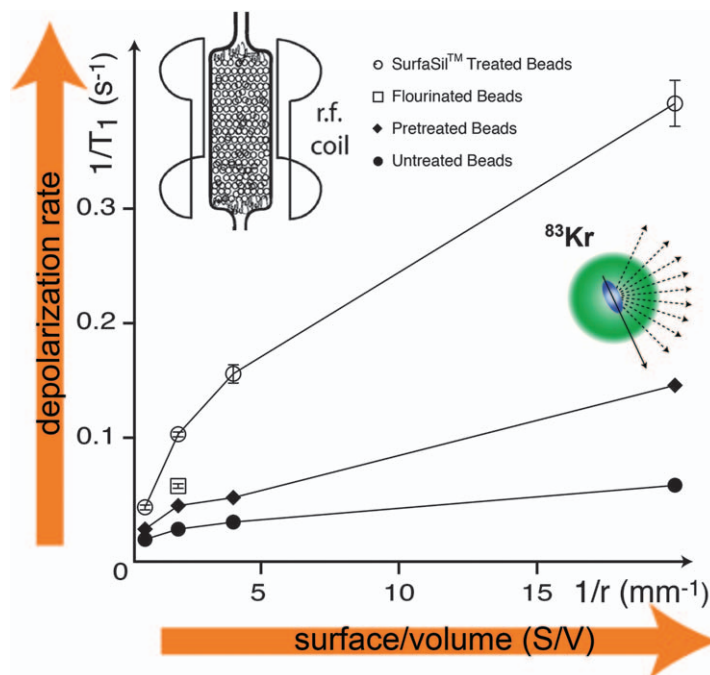


Figure 23.4 Longitudinal ^{83}Kr relaxation rates $1/T_1$ in a model surface system made from uniform sized glass beads – see schematic, upper left. Different surface to volume ratios (S/V) are produced through different glass bead radii, r , ranging from 0.05 mm to 1.25 mm. Different surface chemical affinities are obtained through treatments as indicated. The relaxation rates are shown as a function of the inverse glass bead radius $1/r$ that is (approximately) proportional to S/V . The relaxation increases with rising $1/r$ values, and therefore increasing S/V . The relaxation rate also accelerates with increased surface hydrophobicity. Adapted from ref. 39 with permission. Copyright 2006 Elsevier.

model surfaces with different surface to volume ratio, as S/V is inversely proportional to the radius of the beads, $S/V \propto r^{-1}$, assuming approximately close-packing of identical beads (note the largest beads will arrange less ideally within the small container). Furthermore, the beads were exposed to various surface treatment to assume either more hydrophilic or more hydrophobic properties. Independent of surface treatment, observed $1/T_1$ relaxation rates, shown in Figure 23.4, clearly increased with increasing S/V .³⁹ Independent of the S/V , faster ^{83}Kr T_1 relaxation is found on surfaces with higher adsorption enthalpy for the non-polar krypton atoms, *i.e.* hydrophobic surfaces, compared to the relaxation observed with hydrophilic surfaces. Therefore, ^{83}Kr gas phase relaxation can be used for MRI contrast of the surface chemical composition, as demonstrated in ref 40. Note that closest packing of 1 mm diameter beads will produce void spaces with dimensions similar to those of human alveoli and this model surface has also been used to explore the effect of pulmonary surfactant.⁴¹

23.3.3 Hyperpolarized ^{83}Kr SQUARE MRI Contrast in Lungs

Although model surfaces can be used to study the underlying physics of ^{83}Kr surface quadrupolar relaxation, they cannot substitute for real lung surfaces. To enable pulmonary ^{83}Kr SQUARE NMR and MRI studies within the setting of a physics laboratory, a special ventilation chamber was developed.⁴² Excised rat lungs were placed in an artificial pleural cavity, as shown in Figure 23.5. The lungs were placed, submerged in isotonic saline solution, with the apex pointing downwards and the trachea was sutured to an adapter tube affixed to the bottom of the ventilation chamber. By creating a slight suction in the ventilation chamber, the lungs inflated and were able to inhale the hp ^{83}Kr delivered to a storage container below the ventilation chamber. The lungs therefore were able to actively inhale the ambient pressure hp gas.

Using a series of small flip angle NMR experiments, the hp ^{83}Kr signal was monitored as the gas was inhaled and the hp ^{83}Kr relaxation was measured during the subsequent breath hold.⁴³ The semi-logarithmic data representation demonstrates mono-exponential relaxation behavior for an approximate 2.5 s duration. The relaxation times were investigated as a function of inhalation volume, but here it suffices to state that $T_1^{^{83}\text{Kr}} \approx 1\text{ s}$ for ^{83}Kr within the alveolar region of the rodent lung. This is a promising value for *in vivo* studies as the breathing frequency is about 1 Hz for rats in the resting state. Note that longer relaxation times are to be expected for human lungs that have larger alveoli and therefore, presumably, lower S/V . Note also that the presence of up to 40% O_2 did not affect the ^{83}Kr relaxation in the rat lungs.

At longer times of breath hold, the hp ^{83}Kr signal in Figure 23.5 depolarizes at a slower rate. This effect is caused by hp ^{83}Kr contained in the airways that have a reduced S/V compared to the alveolar region. Slower relaxation in the airways can clearly be observed in the slice selective hp ^{83}Kr MRIs, shown in Figure 23.6a–d that have become feasible after significant improvements in the SEOP technology.^{38,44} Using different delay times after inhalation and before the images are recorded, the relaxation can be monitored. The resulting T_1 map (Figure 23.6e) depicts the actual SQUARE contrast.

In current work hp ^{83}Kr MRI SQUARE contrast is being applied to identify the S/V changes in an elastase animal model of emphysema. Further developments in the hp ^{83}Kr MRI protocol continue to advance the quality of the images. In other approaches, higher laser power and a modified SEOP procedure are being explored to enhance the polarization P and in particular the apparent polarization P_{app} .

Two aspects associated with hp ^{83}Kr MRI appear, at a first glance, to defy ‘common MRI wisdom’: (1) the very low ^{83}Kr resonance frequency (*i.e.* 4.9 MHz at 3 T) is very unusual but it is not a major concern for detection as hyperpolarized gas is used. The low gyromagnetic ratio can also be advantageous as it significantly reduces the relaxation caused by

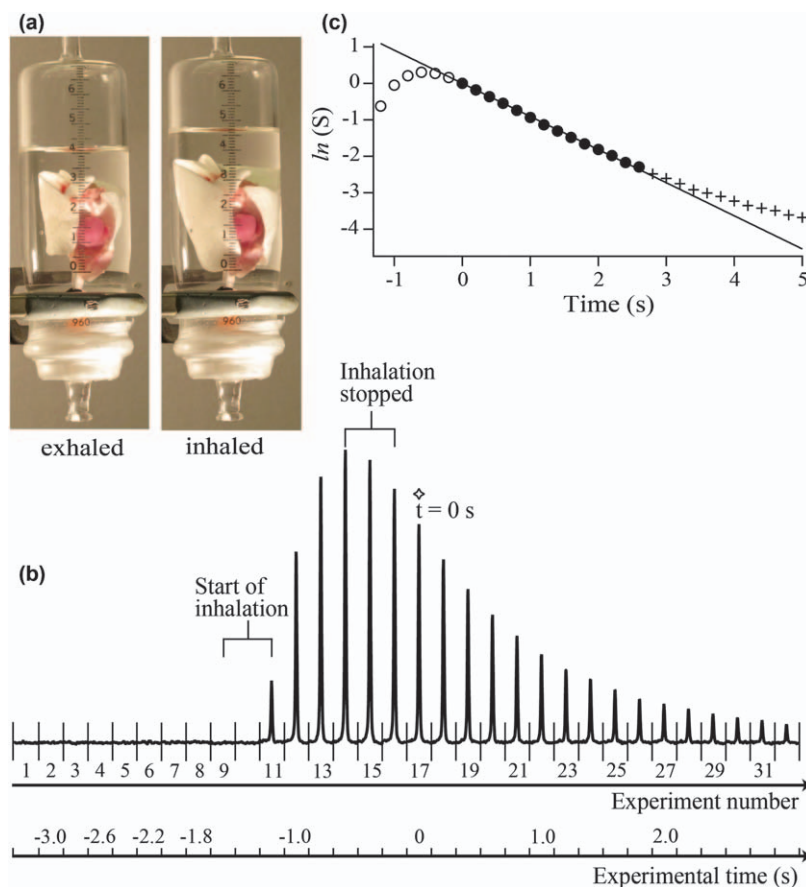


Figure 23.5 Concept of hp ^{83}Kr relaxation measurement in excised rat lungs. (a) Excised rat lung submerged (upside down) in isotonic saline solution with main trachea attached to glass tube exiting the chamber at the bottom. Inhalation and exhalation is enabled through the application of a small suction or over pressure within the cylinder above the solution. (b) Result from small flip angle NMR experiment monitoring the hp ^{83}Kr gas inhalation into the lung. The signal intensity initially rises because of hp ^{83}Kr entering the lung. It then decays due to relaxation causing depolarization. The focus is on the initial depolarization shortly after breath hold ($t = 0$ s) that provides the T_1 relaxation time of ^{83}Kr in the lung. (c) Semi-logarithmic plot that visualizes the time span of the mono-exponential behavior of ^{83}Kr relaxation. Adapted from ref. 43, © Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved.

paramagnetic oxygen. It also reduces the adverse effects of magnetic susceptibility for transverse relaxation. (2) Depolarization is generally considered to be disadvantageous for MRI with hyperpolarized spin systems, however it can also be utilized for novel sources of contrast as exemplified with SQUARE.

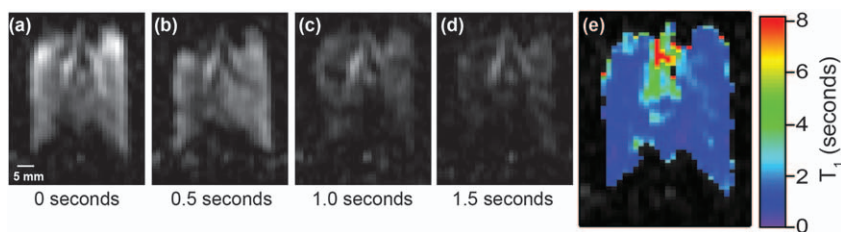


Figure 23.6 Hp ^{83}Kr MRI of surface quadrupolar relaxation (SQUARE). (a) MRI taken immediately after inhalation of hp ^{83}Kr . (b)–(d) Images are acquired with a delay time (indicated below the images) between inhalation and MRI acquisition. The delay time allows for some hp ^{83}Kr relaxation to take place that is slower in the airways (lower S/V) compared to the parenchymal region with higher S/V . (e) ^{83}Kr T_1 SQUARE MRI calculated from (a)–(d).

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Krypton gas has already been used in human subjects for dual energy CT (DECT)⁴⁵ and does not have anesthetic properties at the quantities required for MRI. One of the main current obstacles is the high cost of isotopically enriched ^{83}Kr , *i.e.* about 4000 € per litre gas at ambient pressure, however the gas can easily be recycled to reduce costs. Furthermore, this price mostly reflects the low stockpile of the purified isotope at present. Like xenon, natural abundance krypton is a renewable resource that is obtained from air liquefaction.

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Beyond Spin Exchange Optical Pumping: Hyperpolarization of ^{129}Xe via Sublimation Dynamic Nuclear Polarization

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24.1 Hyperpolarization *via* Dynamic Nuclear Polarization

24.1.1 Concept

To enhance nuclear magnetic resonance (NMR) signals, it is possible to take advantage of the large polarization of electron spins, essentially 1 (or 100%) at a temperature of around 1 K and in a field of a few Tesla (the ^{129}Xe polarization in the same conditions is on the order of 0.1%). Dynamic

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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nuclear polarization (DNP) consists of transferring the large electron spin polarization of incorporated free radicals to the surrounding nuclei in a frozen sample by continuous irradiation with microwaves close to, but not exactly at, the electron spin resonance (ESR) frequency of the free radicals. This technique which was developed in the realm of particle physics became of great interest for liquid-state NMR and magnetic resonance imaging (MRI) following the introduction of an inventive dissolution step to transform the frozen sample into a liquid using a hot solvent.¹ Hyperpolarization *via* the so-called dissolution DNP method increases NMR sensitivity by 3–4 orders of magnitude and offers the opportunity to perform real-time NMR spectroscopy experiments.

24.1.2 Biomedical Applications of Dissolution DNP

The introduction of dissolution DNP has opened new perspectives in biomedical NMR research. The tremendous gain in signal-to-noise ratio (SNR) resulting from hyperpolarization techniques makes it possible to non-invasively probe fast biochemical transformations from ¹³C- or ¹⁵N-labeled precursors to metabolic products. This technique can be applied to study metabolism *in vitro* in cells in order to measure fluxes through metabolic pathways in real time in controlled environments. With a typical time resolution of one second, metabolic imaging *in vivo* can be essentially performed in real time.² Hyperpolarized (HP) substrates prepared *via* dissolution DNP have been proposed as MRI contrast agents for cancer or cardiac failure diagnosis and therapy monitoring through the detection of metabolic impairments *in vivo*.^{3–5} The results of the first human study performed on prostate cancer patients were recently published and it was shown that metabolic dysfunctions associated to cancer cells were detected in regions that were considered tumor-free following examination with conventional anatomic imaging modalities.⁶ These applications have driven a spread of this technology within the NMR and MRI communities in the recent years, in particular in biomedical research laboratories.

24.2 Sublimation DNP

24.2.1 Motivation

The unique chemical, biological and even therapeutic properties of HP ¹²⁹Xe push the limits of molecular MRI far beyond what is achievable with proton relaxivity-based contrast agents or even other HP compounds.⁷ Spin exchange optical pumping (SEOP) has demonstrated its efficiency as a dedicated method to hyperpolarize ¹²⁹Xe.⁸ In batch mode (“stopped flow”) or continuous flow, using portable and compact systems or large-scale production setups, it can produce highly polarized gas under optimal conditions, but large throughput (1–2 L per hour of xenon gas at

atmospheric pressure) is often synonymous with less favorable conditions limiting the maximum achievable polarization level.^{9,10} With the development of dissolution DNP and its dissemination in clinical and preclinical environment, it is of great interest to have a method to hyperpolarize ^{129}Xe using the same generic dissolution DNP hardware already available to hyperpolarize a variety of HP compounds, mostly ^{13}C -labeled substrates, for metabolic or molecular imaging applications. As the DNP process takes place at low temperature, the volume of HP gas that can be produced within a relatively small sample space volume is large (the expansion coefficient from solid to gas at 1 atm and room temperature is about 530). The perspective offered by the production of large volumes of HP gas using a generic hyperpolarizer was the main motivation for developing the technique described in the following sections.

24.2.2 Concept

A method to extend hyperpolarization *via* DNP to the production of room-temperature hyperpolarized gases was proposed by Comment *et al.* and demonstrated with xenon.¹¹ The idea is to condense xenon in its liquid phase, admix free radicals in a homogenous manner, and freeze the mixture before polarizing the xenon spins *via* DNP. Once polarized, a sublimation procedure is used to extract the hyperpolarized gas from the polarized solid-state sample. The sublimation DNP method being similar to dissolution DNP, it can be performed using the same hyperpolarizer although some additional specific hardware parts are required for the collection and storage of HP ^{129}Xe . If a solvent is used for the sublimation process, the hyperpolarized gas has to flow through a leak-tight separator that will collect the solvent. In addition, since the sample is immersed in liquid helium during the DNP process and the hyperpolarized gas is usually pushed out of the polarizer with helium gas, the hyperpolarized gas has to be separated from helium gas. This is done by flowing the gases through a classical liquid nitrogen cold trap (*i.e.* cryo-collection). The hyperpolarized xenon gas will solidify while helium gas will flow through and be removed from the system. Note that the system might be contaminated with traces of nitrogen gas but N_2 will also be pushed out of the cold trap with the helium gas. A schematic diagram of the extraction process is presented in Figure 24.1.

The maximum achievable ^{129}Xe polarization that has been so far achieved *via* DNP was mostly limited by the preparation procedure used to obtain homogenous solid-state samples. Values on the order of 5% were typically reported.^{11,12} The highest value reported in customized hardware conditions using enriched ^{129}Xe combined with a temperature cycling procedure was about 21% but it took more than 16 h to reach this level.¹² The key parameters in the preparation of optimized frozen xenon samples for sublimation DNP are discussed below.

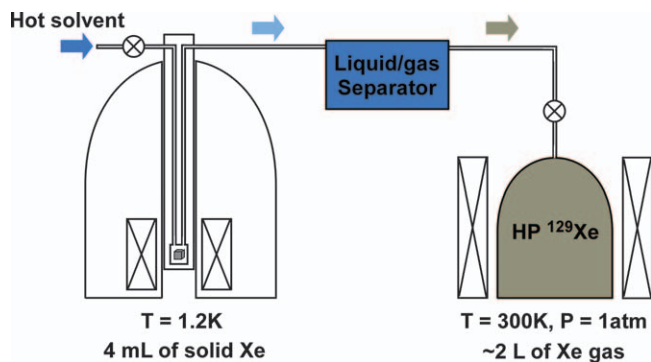


Figure 24.1 Schematic representation of the extraction process of HP ^{129}Xe in the sublimation DNP method.

24.2.3 Solid-state Xenon Samples

24.2.3.1 Radical-doped Glassy Matrix

For the DNP process to be efficient, the free radicals have to be homogeneously distributed in the frozen solution containing the molecules of interest. Since the radical concentration required for DNP is rather large (typically on the order of tens of mM), it is generally not possible to dissolve the free radicals directly into the non-polar liquid xenon. Rather, a solvent is used to introduce the usually persistent radicals into the frozen sample. The triple point of xenon occurs at 161.4 K and 81.6 kPa. To dissolve nitroxide radicals such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), which is commonly used in DNP (see discussion below), we chose 2-methylpropan-1-ol (isobutanol) because of its low freezing point of 165 K, which is only 3.6 K above the xenon triple point. At a pressure of 500 kPa, the temperature range in which both xenon and 2-methylpropan-1-ol are in their liquid phase is on the order of 30 K.

To prepare a 2 mL glassy frozen sample with a final radical concentration of 50 mM, the procedure was as follows: first, 1 mL of 2-methylpropan-1-ol doped with 57 to 86 mM TEMPO was incorporated into a home-built cold finger with a graduated glass. The cold finger was pressurized to between 100 and 500 kPa with xenon gas (natural isotopic abundance (26% of ^{129}Xe) in the present study) and the bottom of the cold finger was slowly placed in a cell cooled by cold nitrogen gas. Once the cold finger reached a temperature of about 170 K, liquid xenon flowed into the TEMPO-doped 2-methylpropan-1-ol solution. After intermittently agitating the mixture using a magnetic stirrer, a solution containing 50 mM of TEMPO was obtained. The solution was then frozen by plunging the cold finger into liquid nitrogen, and the glassy frozen sample was extracted from the cold finger before its transfer to the sample holder of the polarizer. The resulting matrix can be, depending on the xenon concentration and the chosen solvent, a heterogeneous assembly of xenon dissolved in

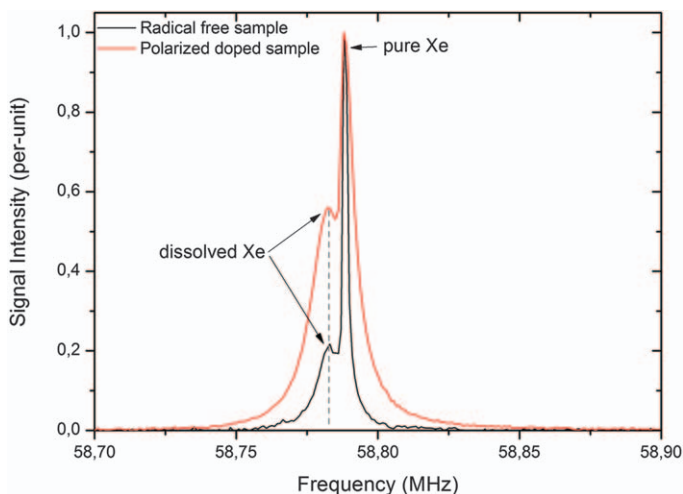


Figure 24.2 Normalized ^{129}Xe NMR spectra measured at 1.5 K in a sample containing 2-methylpropan-1-ol doped with 50 mM TEMPO radical and 9.4 M of natural isotopic abundance xenon (red curve; maximum polarization of 2.5% obtained after 60 min while irradiating with 55 mW at 140.3 GHz), and in a thermally polarized sample of the same composition but without radical.

the radical doped glassy matrix and pure xenon clusters as described by Kuzma *et al.*^{12,13} The typical NMR spectrum presented in Figure 24.2 illustrates this separation into two compartments with dramatically different behaviors.

24.2.3.2 The Choice of Glass-forming Solvent

^{129}Xe polarization strongly depends on the characteristics of the glass-forming solvent, namely the maximum concentration of xenon that can be dissolved in the solvent, and the chemical shift difference between pure xenon and dissolved xenon in the solid state. As an illustration, we present in Figure 24.3 the systematic study we performed as a function of the xenon concentration incorporated in samples prepared with 2-methylpropan-1-ol.

In an optimal 0.65 mL sample composed of 5 M of natural isotopic abundance Xe gas dissolved in 2-methylpropan-1-ol doped with 50 mM TEMPO, the maximum ^{129}Xe polarization obtained at 1.2 K in a 5 T custom-designed DNP polarizer^{15,16} was 13% after 80 min of microwave irradiation at 140 GHz with 50 mW power, using a standard smooth-wall waveguide. The volume of natural isotopic abundance xenon gas that can be extracted from this frozen sample is about 100 mL.

Ethanol as well as 1-propanol have also been used as solvents to form a glassy frozen matrix containing xenon.¹² Although nitroxyl radicals are readily dissolved in ethanol, the amount of xenon that can be incorporated

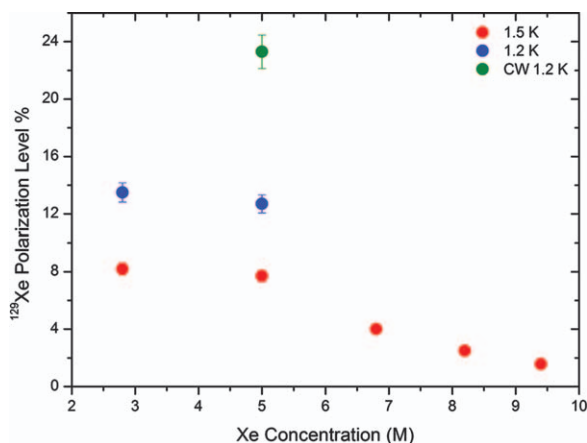


Figure 24.3 Maximum solid-state ^{129}Xe polarization obtained in a sample containing 2-methylpropan-1-ol doped with 50 mM TEMPO as a function of xenon concentration for different conditions ($T=1.5$ K or $T=1.2$ K using a smooth-wall waveguide, and $T=1.2$ K using a corrugated waveguide).

in this polar compound is limited compared to what can be dissolved in 2-methylpropan-1-ol because of the shorter carbon chain of ethanol. In addition, the chemical shift difference between ^{129}Xe dissolved in ethanol and pure solid ^{129}Xe is 204 ppm compared to 85 ppm for 2-methylpropan-1-ol. These larger chemical shift differences reduce the probability of flip-flop transitions between ^{129}Xe spins from the two different compartments, especially at high magnetic field, and therefore limits the spin diffusion process necessary to homogeneously and efficiently polarize the ^{129}Xe spins across the entire sample volume. The ideal solvent would have a low freezing temperature, close to the xenon triple point, incorporate a large volume of xenon, and lead to a small chemical shift difference between dissolved ^{129}Xe and pure solid ^{129}Xe . It should also not react with the radicals dissolved in it.

The DNP efficiency could be further improved by an adequate isotopic composition of the glass-forming solvent. It has been shown that deuteration of the glass-forming solvent yields double the ^{13}C polarization in samples doped with nitroxyl radicals at 3.35 T and 5 T,^{17,18} but complete solvent deuteration seems to be detrimental to the maximum ^{13}C polarization at 7 T.¹⁹ Thus, further studies are required to validate to what extent partial or complete deuteration of the glass-forming solvent will lead to a potential gain in ^{129}Xe polarization at the chosen working field. Note that in the context of biomedical and clinical use, the matrix in which xenon is incorporated does not have to be biocompatible since xenon is extracted in its gas form after the DNP process. Indeed, unlike for dissolution DNP, the solvent and spins of interests will be automatically separated during the sublimation process.

24.2.3.3 The Choice of Free Radical Species

The sublimation DNP method was originally developed using nitroxyl radicals (namely TEMPO), but a large variety of persistent or photo-induced radicals might meet the requirements needed for efficiently hyperpolarizing ^{129}Xe . The narrow ESR line width of trityl radicals leads, in dissolution DNP, to the highest ^{13}C polarization levels.²⁰ For sublimation DNP, Kuzma *et al.* measured a ^{129}Xe polarization level (in natural isotopic abundance xenon) of about 5%,¹² *i.e.*, an essentially identical value than the one obtained with TEMPO.¹¹ Additional comparative studies or theoretical developments in the context of ^{129}Xe sublimation DNP are needed to properly evaluate the potential added value of using trityl radicals.

It has been recently shown that non-persistent radicals can be produced by mean of ultraviolet (UV) irradiation of solid-state samples containing pyruvic acid (PA).²¹ We also demonstrated that photo-induced radicals can be formed in glassy frozen xenon samples.¹⁴ The samples were prepared by mixing PA (as radical initiator), a glass-forming solvent (*e.g.* ethanol or 2-methylpropan-1-ol), and liquid xenon at natural isotopic abundance. The frozen samples were plunged in liquid nitrogen and UV irradiated using a commercially available UV LED source for 1 h and then polarized in a custom-designed dissolution DNP polarizer operating at 1.2 K and 5 T. The first results demonstrated that a polarization value of 15% can be achieved.¹⁴ This improved polarization is most likely due to the narrow ESR line width of the obtained radicals and a homogenous radical distribution within the frozen sample.

24.2.3.4 Natural Isotopic Abundance vs. ^{129}Xe -enriched Xenon

In the solid-state, both the ^{129}Xe and ^{131}Xe spins are polarized, but only the spin 1/2 of ^{129}Xe has a long enough relaxation time to maintain its polarization through the gas extraction process, and the spin 3/2 ^{131}Xe relaxes back to its Boltzmann equilibrium polarization by the time the hyperpolarized gas is collected. The presence of the ^{131}Xe spins, however, plays an important role in the DNP process. In a model of thermal mixing, the spin temperature of each nuclear species is the same and spin diffusion depends on the concentration and type of nuclear magnetic moments present in the sample. The gyromagnetic ratio of ^{131}Xe is about 3.4 times lower than for ^{129}Xe but their natural isotopic abundance is similar. Using ^{129}Xe -enriched xenon would thus be advantageous in terms of concentration and polarization efficiency since it would remove the thermal load imposed by ^{131}Xe spins. The effect has been discussed when deuterated solvents are used instead of protonated solvents in dissolution DNP.¹⁷ Hyperpolarization of ^{129}Xe by DNP using ^{129}Xe -enriched xenon has been performed and discussed by Kuzma *et al.* and they observed a 3-fold increase in solid-state ^{129}Xe polarization.¹²

24.2.4 Hardware Optimization

24.2.4.1 Large Samples for Increased Volumes

It has been shown that a solid-state sample volume as large as 8–9 mL can be polarized *via* DNP resulting in, following dissolution, more than 100 mL of aqueous solution containing a high concentration of HP compounds.²² Only small modifications of the hardware are required to insert such a large sample inside the hyperpolarizer. If used for ^{129}Xe sublimation DNP, such a setup would allow for the production of more than 2 L of hyperpolarized xenon at atmospheric pressure without significantly affecting the achieved polarization level and polarization time. This is of major interest for potential clinical applications of hyperpolarized xenon in lung imaging or for a centralized production of HP ^{129}Xe .²³ The main technical challenge that will need to be addressed for multi-litre production of hyperpolarized gases will be the handling of the large volume of gas that will result from the sublimation process, although this problem is merely a technical problem and solutions have already been proposed in the context of SEOP based hyperpolarization of ^{129}Xe .

24.2.4.2 Corrugated Waveguide for Increased Output

We have also recently developed a corrugated waveguide in collaboration with the start-up company SwissTo12 to minimize the microwave losses and

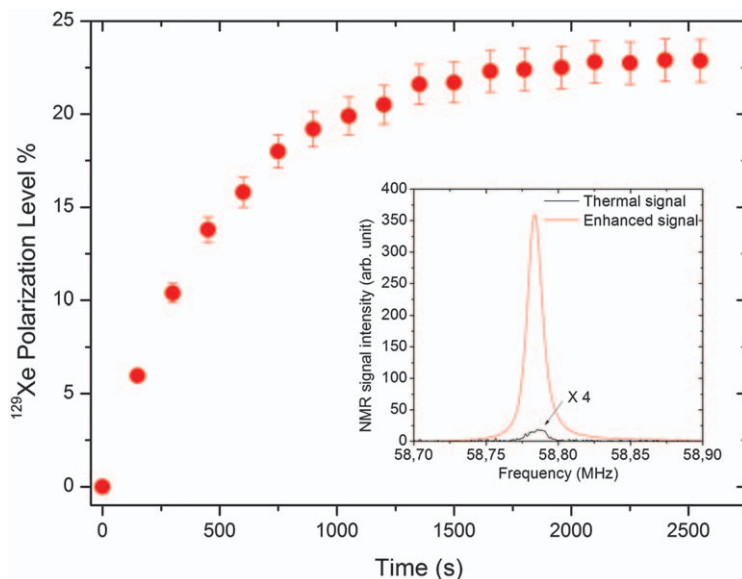


Figure 24.4 ^{129}Xe polarization as a function of time recorded during DNP at 1.2 K and 5 T preformed with a corrugated waveguide in a sample containing 2-methylpropan-1-ol doped with 50 mM TEMPO and 5 M natural isotopical abundance xenon. The corresponding ^{129}Xe NMR spectra at thermal equilibrium (black curve) and after 2500 s of DNP (red curve) are presented in the inset.

study the effect of the microwave polarization on the DNP process. Our initial results demonstrated that the ^{13}C polarization obtained at 5 T and 1.2 K can be up to two times larger with the corrugated waveguide than with a usual smooth-wall waveguide. The maximum ^{129}Xe solid-state polarization was observed in a glassy matrix of 2-methylpropan-1-ol doped with 50 mM TEMPO and containing 5 M natural isotopic abundance xenon using a 140 GHz corrugated waveguide and about half the microwave power, and reached about 25% in about 30 min (Figure 24.4).

24.3 Conclusion and Outlook

To benefit from the wide-scale dissemination of the dissolution DNP technology, in particular in biomedical NMR/MRI environment, the sublimation DNP method has been proposed to hyperpolarize ^{129}Xe using generic dissolution DNP hyperpolarizers. Recent developments have shown that the maximum ^{129}Xe polarization level and moreover “usable ^{129}Xe magnetization” obtained by sublimation DNP is comparable to what can be obtained with the well-established SEOP techniques. The HP xenon gas throughput can be larger with sublimation DNP than with standard SEOP systems and the volume of gas that can be produced within a half hour can be sufficient for the standard current applications of HP ^{129}Xe . Further developments, including the identification of photo-induced radicals initiators that could be directly dissolved in liquid xenon and hardware optimization for improving the ^{129}Xe polarization beyond the 25% already achievable, open promising perspectives for sublimation DNP. Far from being an exotic method, sublimation DNP has demonstrated its ability to be a valuable tool for a wider spread of the large variety of powerful applications of the HP ^{129}Xe (as extensively described in this book) in the NMR and MRI community.

Acknowledgements

A. Capozzi and A. Comment are supported by the Swiss National Science Foundation (grant PP00P2_133562).

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CHAPTER 25

Rethinking the Detection Scheme: Hyperpolarized Xenon NMR and MRI Signal Amplification by Gas Extraction and Remote Detection

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25.1 Introduction

Nuclear magnetic resonance (NMR) is a versatile, non-invasive analytical technique, which can be used to obtain information about the spatial and electronic structure as well as the dynamics and mobility of a wide range of molecules and materials. Magnetic resonance imaging (MRI) further enables spatially resolved measurements of any property that is accessible through NMR. The primary handicap of NMR is its inherently low sensitivity when executed in the conventional way by placing a sample in a strong magnetic

New Developments in NMR No. 4

Hyperpolarized Xenon-129 Magnetic Resonance: Concepts, Production, Techniques and Applications

Edited by Thomas Meersmann and Eike Brunner

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Published by the Royal Society of Chemistry, www.rsc.org

field and letting the nuclear spins align according to a Boltzmann distribution. Due to the low density of the nuclei of interest, gas phase NMR and MRI is particularly challenging. To improve the sensitivity, three aspects can be optimized more or less independently: the sample, the pulse sequence used to manipulate the nuclear spins, and the experimental setup.

To optimize the sample, or more precisely the available longitudinal magnetization M_z at the beginning of an experiment, we can maximize the available spin density, increase the external magnetic field B_0 , apply cryogenic temperatures, or apply polarization enhancement techniques. Each of these strategies has clear limitations: magnets with field homogeneities sufficient for NMR are difficult to build with B_0 above 25 T, many samples cannot be cooled to cryogenic temperatures, and the concentration of a sample cannot be increased beyond some maximum value without exerting extreme conditions. Polarization enhancement is an elegant technique, but no generally applicable method exists to date. For noble gases, hyperpolarization by optical pumping has proven to be very successful.¹ Experiments can be performed in batch mode, where some amount of gas is polarized in a first step and then used up during the experiment, or in flow mode, where gas is continuously extracted from the pumping cell and supplied *via* tubing to the NMR cell. This latter approach facilitates the analysis of void space in and fluid flow through porous materials in a straightforward way.²

From a sensitivity aspect, an optimized pulse sequence transfers a maximum of the information-containing magnetization into an observable form and detects it for as long as possible. The vast majority of magnetic resonance experiments are performed by inductively detecting transverse magnetization, using the same coil to excite the spins and to pick up the signal induced by their response. In this case, the optimum sensitivity in a single-repetition experiment is achieved using an on-resonant pulse with a flip angle of 90° . In the general case, it is possible to find a theoretical conversion limit for arbitrary coherences occurring during an NMR experiment, but it is not necessarily straightforward to identify the optimum pulse sequence.³

The possibilities for optimizing the detection hardware are manifold, but it is usually necessary to find a practical compromise between sensitivity, operability and expense. Furthermore, there are often technical or practical limitations for the feasibility of certain optimizations. For example, it is generally unrealistic to build a coil optimized for every sample, especially if a sample cannot be fitted into a standard-size NMR tube. The filling factor of fluid-filled void space of a porous material can be inherently small if the porosity is low. Samples that are magnetic, electrically conducting, or that contain large internal susceptibility gradients are often unsuitable for NMR analysis at high B_0 .

Rather than using the same circuit for excitation and detection, one strategy for improving the NMR sensitivity is to use a different device for detection than for spin excitation. An example is the sensitivity encoding (SENSE) technology,⁴ common nowadays in medical MRI, where an array of smaller, more sensitive surface coils is used for detection, while excitation is

done with a volume coil. Remote detection is another strategy to separate excitation and detection.⁵ Thereby, not only is a different device used for encoding and detection, but the two steps are spatially separated, which opens unprecedented opportunities to optimize both of them individually.

25.2 Concept of Remote Detection

With remote detection, information about a sample of interest is encoded onto a mobile carrier, where it is stored as M_z of nuclear spins. Therefore, the encoded information is protected against dephasing and merely decays with the longitudinal relaxation time constant T_1 . This carrier is extracted from the sample and transported to a more sensitive detector that is tailored to read out its M_z as sensitively as possible.⁵

Suitable carriers are gaseous or liquid fluids, preferably with long T_1 , high density of the information-carrying spin, high nuclear polarization, high gyromagnetic ratio and low chemical reactivity. Hyperpolarized ^{129}Xe gas is ideally suited for this purpose⁶ and was used for the first remote detection experiments.⁵ It is chemically inert, therefore it can get in direct contact with a sample to be studied. Its T_1 is on the order of several minutes unless it is in direct contact with a surface or a molecule that causes it to relax more quickly. Since Xe only occurs at extremely low concentration in the environment, no background signal is detected in the absence of hyperpolarized xenon supplied artificially as part of the experiment. An illustration of remote detection is shown in Figure 25.1, where hyperpolarized ^{129}Xe gas was dissolved in water for encoding and then extracted into the gas phase again for detection.⁷ Since a higher number density of xenon atoms could be achieved in the gas phase, the volume of the detection coil was significantly smaller than the encoding volume. The smaller detection coil allowed for a more sensitive detection of the encoded information than what would be possible in the encoding volume (Figure 25.1b).

The encoding step can consist of an arbitrary pulse sequence that is able to transfer the desired information, for example spectroscopic,⁵ imaging,⁸ flow^{9,10} or relaxation,¹¹ onto the mobile carrier. Any information that can be encoded in a conventional experiment can also be detected remotely, provided that a suitable method can be found for its transfer onto a mobile carrier. In the simplest case, the carrier is itself the substance of interest that would also be detected in a conventional experiment. This is the situation that was most commonly employed to date. Alternative suggestions to encode information onto a mobile carrier include the use of exchange mediated magnetization transfer¹² or the dipolar demagnetizing field.¹³

If the carrier is also the substance of interest, encoding can be done using the same pulse sequence that would be used with conventional detection, but instead of recording of a free induction decay (FID) transiently, transverse magnetization is converted into M_z at one point during the FID.

When studying fluid flow through porous materials, the fluid effluence is an integral part of the experiment already. In this case, remote detection

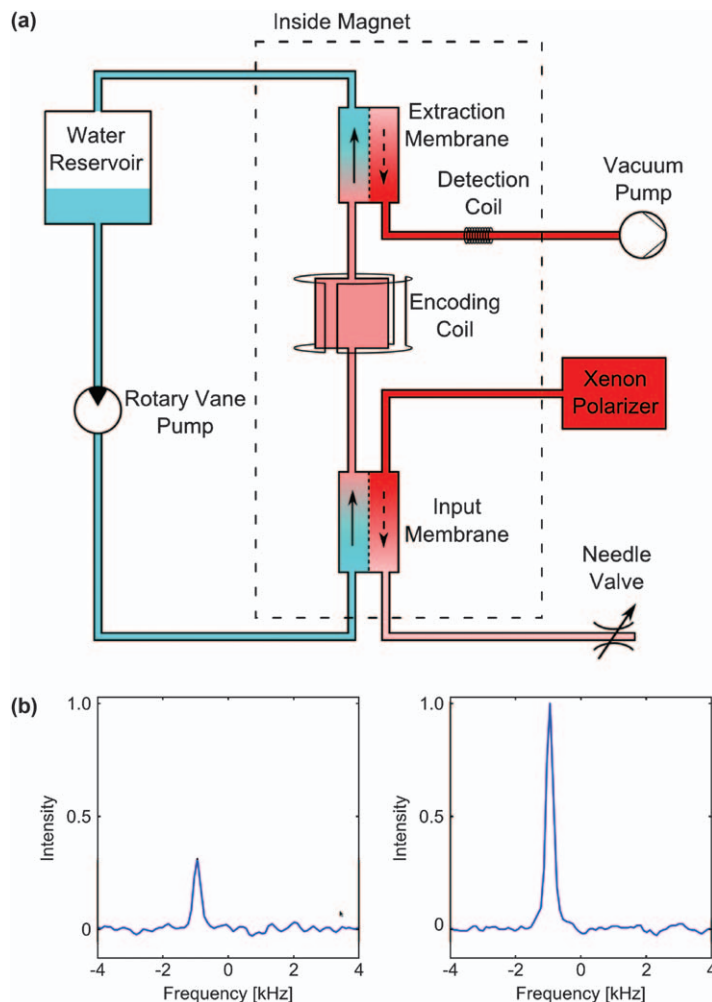


Figure 25.1 Principle of remote detection, illustrated with the *Hyperpolarized xenon Signal Amplification by Gas Extraction* (Hyper-SAGE) experiment.⁷ (a) Schematic of the experimental setup. ^{129}Xe gas is hyperpolarized by spin-exchange optical pumping in the xenon polarizer. Via an input membrane, xenon is dissolved in water that is circulating in a closed loop using a rotary vane pump. After dissolution, the information of interest is encoded onto the nuclear polarization of ^{129}Xe . Using a second membrane, the encoded xenon is extracted into the gas phase. It is then pumped into a detection coil, where the longitudinal magnetization of ^{129}Xe is detected with higher sensitivity than what would be possible using the encoding coil due to the higher density of gaseous ^{129}Xe spins. Therefore, a smaller coil volume for the same number of xenon atoms could be employed for detection. The intensity of the red color represents the concentration of xenon atoms. (b) Experimental example where the NMR spectrum of ^{129}Xe solvated in distilled H_2O is recorded first using the encoding coil with direct detection (left), and then with remote detection using a smaller, volume-matched detection coil (right).

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represents an alternative detection modality that does not even require additional measures for the extraction of the spin sensor from the sample of interest. The only requirement in this case is the availability of an optimized detector at the outlet of the flow setup. A schematic setup with encoding and detection both performed in the sweet spot of the same magnet is shown in Figure 25.2a.

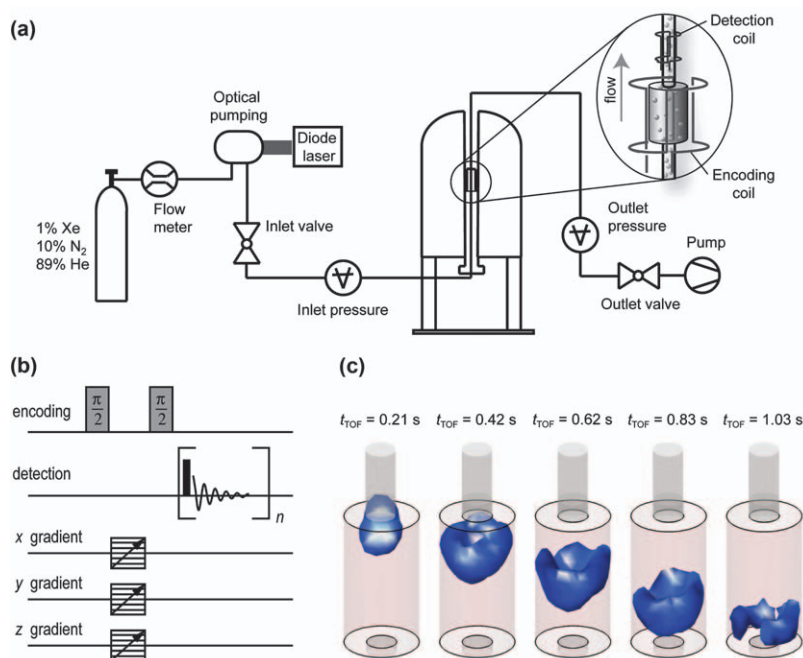


Figure 25.2 Illustration of TOF remote detection. (a) Setup for a high-field experiment where encoding and detection are done in the sweet spot of the same magnet, using hyperpolarized ^{129}Xe as sensor. The encoding coil is large enough to accommodate a porous sample. For time-resolved acquisition, the detection volume, and therefore the size of the detection coil, should be considerably smaller than the volume of the encoded gas, depending on the required temporal resolution. The two coils were part of two different probes. The sample was mounted at the bottom of a Teflon tube that was passing through the detection coil. This probe was inserted into the magnet from the top, while an imaging probe with a hollow bore was inserted from the bottom. In this setup, gas flow is maintained by an overpressure at the gas bottle, and the gas is vented after signal detection. (b) Pulse sequence with three-dimensional image encoding and stroboscopic detection. Each of the three phase encoding gradients is varied independently in subsequent repetitions of the experiment. The second encoding $\pi/2$ pulse converts (stores) transverse magnetization into M_z . The timing is not shown to scale – the encoding step was finished in about 100 μs , while detection pulses were spaced by 50 ms. (c) Isochromal surfaces of gas flowing through a porous Bentheimer sandstone rock, shown at different times t_{TOF} after the encoding step. Gas was flowing from bottom to top.⁹

Table 25.1 Phase cycle for NMR experiments with remote detection to recover the complex signal, thereby enabling quadrature detection along the encoded dimension, and to remove the baseline caused by unencoded fluid in the detector.

Step	Storage pulse phase	Weight
1	$3\pi/2$ ($-y$)	1
2	0 (x)	i
3	$\pi/2$ (y)	-1
4	π ($-x$)	$-i$

A potential issue with remote detection is the signal baseline caused by incomplete encoding of the carrier fluid or unencoded mixing with encoded fluid. This is particularly troubling for imaging applications, as it prevents distinguishing between a baseline and a signal at the origin of the image. This problem can be solved by using a two-step phase cycle to remove signal components with coherence order zero during encoding.

A related issue is the loss of phase information of the encoded magnetization. Since only one component of the complex transverse magnetization M_{xy} can be stored as M_z during each encoding step, another two-step phase cycle is required to encode one complex M_{xy} value. The resulting four-step phase cycle¹⁴ is shown in Table 25.1. Since only the amplitude and sign of M_z is of interest during detection, the recorded data can be reduced to a single value proportional to M_z . This value can then be multiplied with a weight factor instead of changing the detection pulse phase or the receiver phase. Such a procedure is suitable for any detector capable of measuring M_z of the carrier fluid, not just for inductive detection.

Assuming that macroscopic transverse magnetization does not survive the traveling of the fluid between encoding and detection, no phase cycles need to be applied to remove non-zero coherence orders during traveling of the carrier. If this assumption cannot be made, a crusher gradient pulse after the storage pulse could be applied for coherence order selection. Notice that for more complex encoding schemes, it may be necessary to apply further phase cycle steps to remove additional coherence order pathways.¹¹ However, this is generally a consequence of the selected encoding scheme and not a complication caused by remote detection.

25.3 Time-resolved Remote Detection

It is apparent that the main drawback of remote detection is the loss of the transient dimension, since the information is stored as M_z , which only allows acquiring one data point at a time. On the other hand, if the objective of an experiment is to study fluid flow through a porous material, the out-flow of encoded fluid can be measured time-resolved if the detection volume is smaller than the encoded fluid volume. Then multiple detection steps are

required to record all the encoded fluid as it leaves the sample. Rather than just combining the different detection snapshots, each of them can be considered to originate from gas flowing out a certain time t_{TOF} after the encoding step.⁹ This facilitates the correlation between the encoded property, such as position, spectrum or velocity, with the time between encoding and detection. The achievable temporal resolution is on the order of

$$\Delta t \sim \frac{V_d}{\dot{V}} \quad (25.1)$$

where V_d is the fluid volume inside the detector and $\dot{V}$ is the volumetric flow rate. Hence a new transient dimension containing flow information is obtained. With inductive detection, the fluid outflow can be sampled stroboscopically, using a train of 90° pulses spaced by Δt . An example for an image encoding pulse sequence with time-of-flight (TOF) detection, where the signal is recorded as a function time between encoding and detection, is shown in Figure 25.2b, together with an example of gas flow imaging through a porous sandstone rock (Figure 25.2c).

A TOF remote detection experiment is a magnetic resonance equivalent of the tracer injection method used to study flow and dispersion in porous materials, with the difference that the magnetic resonance version is non-invasive and facilitates the tracing of an arbitrary volume element inside the porous sample. TOF remote detection takes an Eulerian view of flow and dispersion.¹⁵ Spins are tagged in one location and then observed as they arrive at another, predefined location in the external laboratory coordinate system. Dispersion is measured in the long-time limit, with local velocity fluctuations of the different fluid elements averaged out over lengthscales set by the dimensions of the porous sample. Thereby, the macroscopic fluid flow is probed. This is in contrast to the Lagrangian viewpoint taken by most of the established pulsed-gradient spin echo techniques, where the displacement of spins from an initial location is probed. Hence, local displacement or velocity distributions are measured directly, which allows one to draw statistical conclusions about the microscopic environment surrounding the fluid molecules. Since the properties measured with the two methods are not easily converted into each other given the limited spatial resolution achievable in magnetic resonance, the two techniques are largely complementary.

For a quantitative description of TOF remote detection, the flow propagator formalism can be employed.^{14,16} Using the conditional probability $P_S(\mathbf{r}_d, t_{\text{TOF}} | \mathbf{r}', 0)$ that a spin located in the infinitesimal volume element $\mathbf{r}'$ during encoding is being located in the volume element $\mathbf{r}_d$ inside the detector at time t_{TOF} , the signal can be calculated as

$$S(\mathbf{r}, t_{\text{TOF}}) = \frac{S_0}{V_d} \int_{\text{detector volume}} d\mathbf{r}_d \int_{\text{encoded voxel}} d\mathbf{r}' \rho(\mathbf{r}') P_S(\mathbf{r}_d, t_{\text{TOF}} | \mathbf{r}', 0) \quad (25.2)$$

S_0 is the signal per unit quantity of spins, ρ is the spin density of the fluid and $\mathbf{r}$ denotes the center of a voxel inside the encoding coil. The two integrals

are necessary since the encoding as well as the detection volume contain a large number of spins and cannot be considered as infinitesimally small. The observed signal is then proportional to an averaged propagator

$$S(\mathbf{r}, t_{\text{TOF}}) = S_0 N(\mathbf{r}) \bar{P}(\mathbf{r}, t_{\text{TOF}}) \quad (25.3)$$

where $\bar{P}(\mathbf{r}, t_{\text{TOF}})$ is the probability for fluid encoded in voxel $\mathbf{r}$ to be in the detection volume at t_{TOF} , and $N(\mathbf{r})$ is the number of spins in the voxel centered at $\mathbf{r}$. From $\bar{P}(\mathbf{r}, t_{\text{TOF}})$, the flow profile of a fluid can be deduced,¹⁶ and conclusions regarding the effective porosity, the macroscopic mean flow velocity or the flow path can be drawn.¹⁴ Furthermore, it is possible to derive connectivities within porous media¹⁷ or to determine desorption time constants.¹⁸

In Figure 25.3, flow and dispersion of xenon gas in microporous silica aerogel is illustrated. It is possible to distinguish between free gas and xenon adsorbed on the surface of the aerogel since ^{129}Xe shows a measurable chemical shift difference between the two phases (Figure 25.3a). Each of the two peaks can then be excited selectively in individual experiments, and chemical shift selective images and flow profiles can be determined. From Figures 25.3d and e, which show the desorption time constant and t_{TOF} at which $\bar{P}(\mathbf{r}, t_{\text{TOF}})$ is maximum, respectively, it can be seen that the porosity

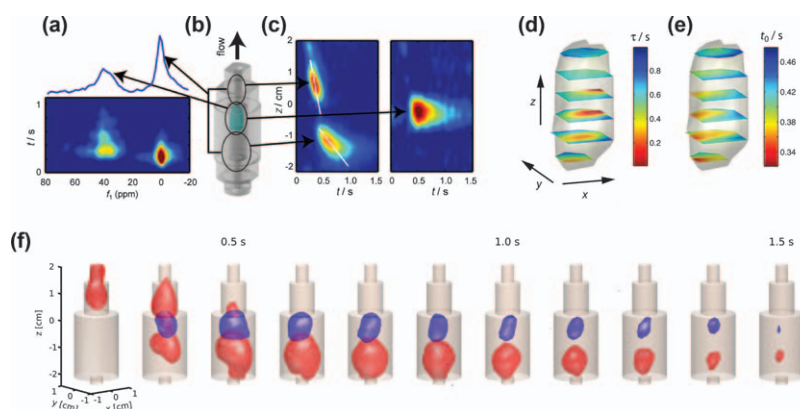


Figure 25.3 Hydrodynamic dispersion of gas flow through porous silica aerogel. (a) Time-of-flight vs. spectrum of ^{129}Xe . Adsorbed on the aerogel surface, ^{129}Xe shows a different chemical shift than in the gas phase (set to 0 ppm). (b) Geometry of the sample holder containing the aerogel (green color). (c) Chemical shift selective projection of ^{129}Xe spin density along the flow direction vs. TOF. The two panels show the dispersion of free gas (left) and gas that was adsorbed on the aerogel surface (right) during the encoding step. (d) Time constant for the release of adsorbed or occluded xenon. (e) Maximum of flow propagator. (f) Visualization of flow, showing the location of free gas (red) and adsorbed (gas) as a function of time between encoding and detection. Panels (a) to (e) adapted with permission from ref. 18. Copyright 2006 Nature Publishing Group.

within the sample is not uniform. Desorption at the outlet of the sample is considerably slower than at the inlet. From Figure 25.3f, it can be inferred that a considerable part of the xenon passes through the sample without getting adsorbed or occluded in the pore space, since most of the gas at the inlet of the aerogel sample shows a shorter t_{TOF} than gas adsorbed on the aerogel surface with a nominally shorter flow path. This indicates the presence of well-connected pores throughout the sample.

In a similar experiment, remote detection with hyperpolarized ^{129}Xe gas had been used to study gas flow through a porous wood sample before and after heat treatment.¹⁷ It was found that the flow resistance did not change drastically by the treatment and that flow was in the direction of the year rings. However, the flow pattern was altered significantly by a considerable decrease in tortuosity caused by the treatment, as displayed in Figure 25.4. The untreated wood (Figure 25.4a) showed gas occluded in poorly connected channels that was released slowly. The majority of the gas was flowing through the center of the wood block, while the rest appeared weakly vented. After heat treatment, a different flow pattern emerged (Figure 25.4b). It was possible to identify the year ring pattern in the sample from the TOF data. Flow was unbranched along the springwood region of each ring, with little or no links between neighboring rings, confirming that the heat treatment closes off a large amount of lateral pits. There was no apparent difference in

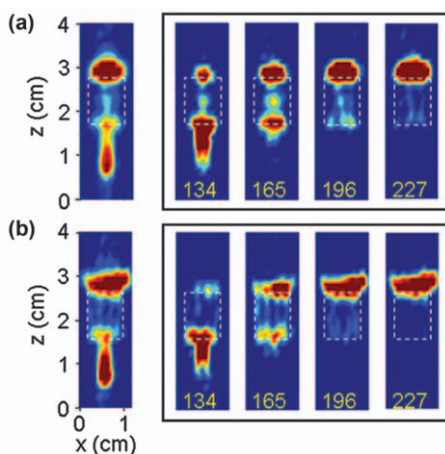


Figure 25.4 TOF experiment to visualize gas flow through *Pinus sylvestris* pine wood sample. The dashed square in the panels shows the position of the wood sample. The panels on the left-hand side show the sum of the individual images acquired during the experiment. It represents a spin density map of all the gas flowing through the detector within the total detection duration. The panels surrounded by a black box represent TOF snapshots of gas present in the detection volume a certain time after encoding. The time in ms is shown at the bottom of each panel. (a) Untreated wood sample. (b) Thermally modified sample. Adapted with permission from ref. 17. Copyright 2009 Elsevier Inc.

flow between year rings – each year ring seemed equally vented. At the same time, it appears that the cell wood structure was partially destroyed to open up better connected longitudinal paths that were not available in the untreated wood.

25.4 Auxiliary Probe Design

When detection is done inductively, which was the case for most experimental implementations of remote detection using hyperpolarized ^{129}Xe gas, two different coils are required, and pulse schemes needed to be split into an encoding and a detection part. To maintain a high flexibility for the setup, it is desirable that samples with different shape and size can be studied without the necessity to construct or modify a probe for each sample geometry. The use of an auxiliary remote detection probe in combination with a commercial, general purpose probe for encoding proved to be a practical and versatile strategy.¹⁹ In Figure 25.5a, it is shown how a microfluidic chip was mounted on such an auxiliary probe, containing a microcoil for detection. This probe could be inserted from the bottom into a microimaging probe with a hollow bore such that the microfluidic chip was located inside its coil for encoding. Encoding and detection coils are both located in the sweet spot of the same magnet. However, due to the small volume of the flow channels and the correspondingly low number of spins, the encoding coil, which had to be large enough to accommodate the whole chip, was not sensitive enough for signal detection.

A crucial aspect was an effective shielding of the two coils from each other. Otherwise the receiver circuit could be damaged by a strong encoding pulse, or systematic errors could be induced by a detection pulse transmitted to

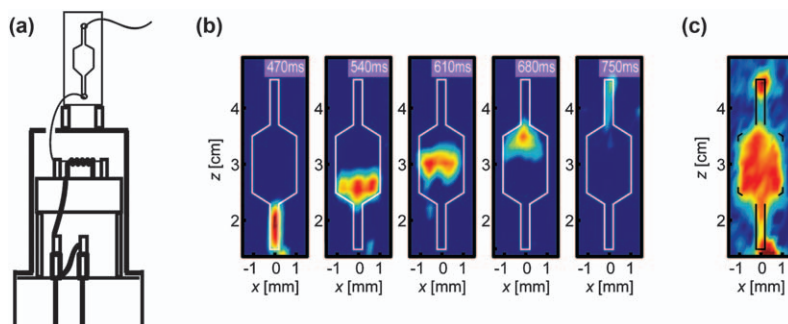


Figure 25.5 Remote detection of gas flow in a microfluidic device with a channel depth of $50\ \mu\text{m}$. (a) Setup with microfluidic chip mounted on an auxiliary probe that was inserted into the hollow bore of a commercial microimaging probe.¹⁹ (b) TOF flow profiles at different t_{TOF} (indicated at the top of each panel). (c) ^{129}Xe image obtained by summing the different TOF snapshots.

Panels (b) and (c) adapted with permission from ref. 10. Copyright 2005 National Academy of Sciences, USA.

encoded fluid prior to its detection. In the probe shown in Figure 25.5a, shielding was achieved by encasing the detection coil in a copper cover with only a small hole for the gas flow tubing.

25.5 Sensitivity

25.5.1 General Formalism

When a sample is placed in a static magnetic field, the different spin states are populated unevenly if the sample was given enough time to reach thermal equilibrium. This imbalance is responsible for the macroscopic magnetization M_0 , which is directly proportional to the observed signal. Alternatively, the relative population of the states, referred to as polarization P , can be used to discuss changes of the measured signal. The sensitivity of an experiment can be quantified using the signal-to-noise ratio ψ . However, ψ does not take into account that different experimental strategies or detection modalities can take a very different amount of time. Since measurement time can be compensated with signal averaging, a more balanced measure to compare the sensitivity of different experimental strategies is the signal-to-noise ratio per square root of time,

$$\Psi = \frac{S}{\sigma\sqrt{T_{\text{tot}}}} = \frac{\psi}{\sqrt{T_{\text{tot}}}} \quad (25.4)$$

where S is the signal amplitude, σ is the root mean square noise and T_{tot} is the experiment duration.²⁰ To compare sensitivity changes caused by different polarization strategies or setup optimizations, such as using different detectors with remote detection but otherwise identical experiments, ψ leads to somewhat simpler expressions. To compare remote detection with conventional NMR detection strategies where the FID is measured transiently, Ψ needs to be determined for both detection modalities.

25.5.2 Inductive Detection

To illustrate potential advantages and limitations of remote detection, the situation of inductive detection is considered. With inductive detection, the signal-to-noise ratio following an on-resonant 90° pulse is approximately proportional to²¹

$$\psi \propto M_0 V_s K \sqrt{\frac{\omega Q T_2^*}{V_c T}} \quad (25.5)$$

where ω is the Larmor frequency of the spins, T is the temperature and V_c the volume of the detection coil, Q is the quality factor of the detection circuit, V_s is the sample volume, T_2^* is the dephasing time constant of the FID, and K is a coil geometry dependent numerical factor.²² In this equation, physical constants and the noise figure contributed during signal

amplification are disregarded. From eqn (25.5), possibilities to improve the sensitivity of NMR experiments can be deduced. With remote detection, the number of encoded spins and their polarization cannot be increased after the storage of the information as M_z of the carrier. Hence the product $V_s M_0$ remains constant at best for detection. This leaves the coil geometry and the square root term to improve the sensitivity in a remote detection experiment. K cannot be easily predicted and must be determined experimentally or numerically for a particular coil geometry. As a rule of thumb, ψ for a solenoid coil is about a factor 2 to 3 higher than for a saddle-shaped coil.²² Further improvements can be achieved by increasing the amplitude or the homogeneity of B_0 , or by using a circuit with a higher Q , with a smaller V_C or a lower T . The sensitivity of two different detectors can be compared by calculating

$$\Lambda = \frac{\psi_r}{\psi_d} = \frac{t_{90}^d}{t_{90}^r} \quad (25.6)$$

where r and d represent remote and direct detection, respectively. The second equality is based on the principle of reciprocity²² and states that the sensitivity is proportional to the duration t_{90} of a 90° pulse for a given detection circuit.

It is important to notice that for remote detection in its basic form it is only necessary to detect M_z of the carrier rather than a transient interferogram. Hence a wider range of detectors is potentially suitable, such as certain types of magnetometers,²³ magnetoresistive sensors²⁴ or spin-exchange optical detection.²⁵ In this case, ψ_r is simply the SNR with which M_z can be determined.

Since T_{tot} is, in general, very different for direct and remote detection, a balanced sensitivity comparison needs to consider Ψ when comparing the two methods. For the case where an FID is detected, T_{tot} is equal to the repetition time for an experiment with direct detection. With remote detection, T_{tot} is equal to the repetition time times the number of detected data points M . However, there is no loss of the multiplexing advantage with remote detection,²⁶ since encoding is still done in the time domain. Each detected data point contains the signal power of the whole sample magnetization, therefore the total signal, after recording all the data points of the FID one by one, is proportional to M , while T_{tot} scales with the same factor. The noise scales with $\sqrt{M}$, hence Ψ is independent of M . With direct detection, the achievable signal power in one repetition of the experiment is not higher than in a single detection step with remote detection, if identical detectors are assumed. Overall, there is no loss or gain of Ψ by detecting each data point individually, despite the fact that the necessary minimum T_{tot} typically increases drastically with remote detection. This is in exact analogy to two-dimensional (2D) NMR experiments.²⁷ Nonetheless, the timing with remote detection is, in general, different than with direct detection and needs to be taken into account for a sensitivity comparison of the

two methods. Furthermore, decay of M_z due to longitudinal relaxation leads to additional signal loss with remote detection. If t_{trav} denominates the traveling time between the storage pulse and the detection, the signal gets scaled with an additional relaxation term

$$\varrho = \exp\left(\frac{t_{\text{trav}}}{T_1}\right) \quad (25.7)$$

If T_1 is not constant during the carrier transport, then an integration over time from $t=0$ to $t=t_{\text{trav}}$ needs to be performed. To consider a time-dependent T_1 is particularly important when the carrier needs to flow through a porous material with large internal susceptibility gradients, which can be caused by paramagnetic impurities or by magnetic domains in the host lattice. If the average residence time of the fluid in the porous material is approximately constant, the use of a hyperpolarized rather than a thermally polarized fluid has the advantage that the overall contact time with the porous medium after establishing the initial polarization, and therefore the total signal attenuation, does not depend on the encoding location. The closer the encoding location to the fluid outlet, the more relaxation happens prior to encoding, and to first order it can be assumed that $\varrho = 1$.

Simplified expressions for the relative sensitivity achieved with remote and direct detection can be derived for the cases when a transient signal is detected and when the signal is recorded for a single point in time, such as an echo.²⁰ When an FID is detected, then

$$\left[\frac{\Psi_r}{\Psi_d}\right]_{\text{trans}} \approx \frac{\Lambda\varrho}{\sqrt{2}} \sqrt{\frac{T_{2,r}^*}{t_d^{\text{max}}}} \quad (25.8)$$

where $T_{2,r}^*$ is the signal dephasing time constant in the remote detector and t_d^{max} is the duration of the FID. The factor $\sqrt{2}$ must be included since with remote detection two encoding steps are required to record a complex data point, while with direct detection the real and imaginary part can be detected simultaneously.

When an echo is detected, we find

$$\left[\frac{\Psi_r}{\Psi_d}\right]_{\text{pp}} \approx \frac{\Lambda\varrho}{\sqrt{2}} \sqrt{\frac{T_{2,r}^*}{T_{2,d}^*}} \quad (25.9)$$

where $T_{2,d}^*$ is the signal dephasing time constant with direct detection. From these equations, we find that remote detection is worth considering in particular when sensitive detection is not possible in the encoding environment, yet a much more sensitive detection modality would be available at a different location. Furthermore, ϱ should be as close to one as possible, which can be achieved if a fast transfer between encoding and detection location is possible or if T_1 of the carrier is long. Hyperpolarized ¹²⁹Xe is therefore an ideal carrier. In addition, it has a long transverse

relaxation time constant T_2 as well, which enables a long dephasing time constant $T_{2,r}^*$ to be obtained if the detection volume is carefully shimmed.

For NMR at low magnetic field, remote detection offers a particularly significant advantage compared to direct detection. In the original publication of the method, an example was presented where encoding was performed at 4 mT and detection in a different magnet at 4.2 T.⁵ Using eqn (25.5), the sensitivity gain can be estimated to be about two orders of magnitude due to the difference in resonance frequency and the significantly higher Q of the high-field circuit.²⁰

25.5.3 Time-resolved Experiments

In the TOF remote detection experiment, not all of the encoded fluid is detected at once. Instead, volume fractions smaller than the encoded volume are measured as the encoded carrier flows out of the sample and through the detector. For optimum sensitivity, V_C should be adjusted to fit V_S . According to eqn (25.5), if $V_S = V_C$ the achievable signal-to-noise ratio scales with $\sqrt{V_S}$. By splitting V_S into n fractions by reducing V_C to V_S/n , ψ of a single acquisition scales with $\sqrt{V_S/n}$. To retrieve the full signal, n snapshots must be summed up. Assuming that each TOF snapshot contributes the same signal, the total signal-to-noise ratio is scaled by $\sqrt{n}$, as in the case of signal averaging. Therefore, the same sensitivity is obtained as in a single acquisition with a matched detection volume, as long as $T_{2,r}^*$ does not get significantly reduced. Only in the limit of very high time resolution, when Δt is much shorter than $T_{2,r}^{*,static}$ without gas flow, the dephasing time with gas flow becomes $T_{2,r}^* \sim \Delta t$ and the sensitivity of the summed up encoded information scales proportionally to $\sqrt{\Delta t/T_{2,r}^{*,static}}$.

Notice that the sensitivity per unit volume improves for smaller detection volumes. Therefore, if some volume element of an image is predominantly located in one subimage, the respective Ψ_{sub} is better than Ψ for the full image obtained for a single acquisition with matched detection volume or a sum of all the snapshots. This is illustrated in Figure 25.5b and c.¹⁰ In Figure 25.5b, a series of snapshots visualizing gas flow through a microfluidic device for different t_{TOF} is shown. In Figure 25.5c, all the snapshots are combined to obtain the spin density map for the device. While the maximum signal in the spin density map is not significantly larger than in the individual snapshots, the noise scales with $\sqrt{n}$, where n is the number of snapshots added up to obtain Figure 25.5c.

The overall sensitivity gain by using a microcoil with a volume matched to the volume of the encoded fluid or smaller is, in the example of Figure 25.5, about two orders of magnitude compared with direct detection using a coil that can accommodate the whole microfluidic chip.^{10,28}

The weak dependence of the achievable sensitivity on the detection volume, as long as it is smaller than the volume of the encoded fluid, can be

utilized to selectively optimize the sensitivity for a region of interest by summing only these TOF snapshots that contain gas encoded in that volume. An example for such an experiment, where the construction of a matched detection volume would have been difficult, is demonstrated in Figure 25.6.

Gas diffusion across a membrane was studied using a position correlation experiment.¹¹ A pulse sequence (Figure 25.6a) was employed to correlate the position of gas along the y -direction, chosen perpendicular to the direction of a membrane, before and after a certain mixing time τ . The results for membranes with 20 nm and 200 nm pores are shown in Figure 25.6b and c, respectively. From the obtained data, it was possible to estimate a gas

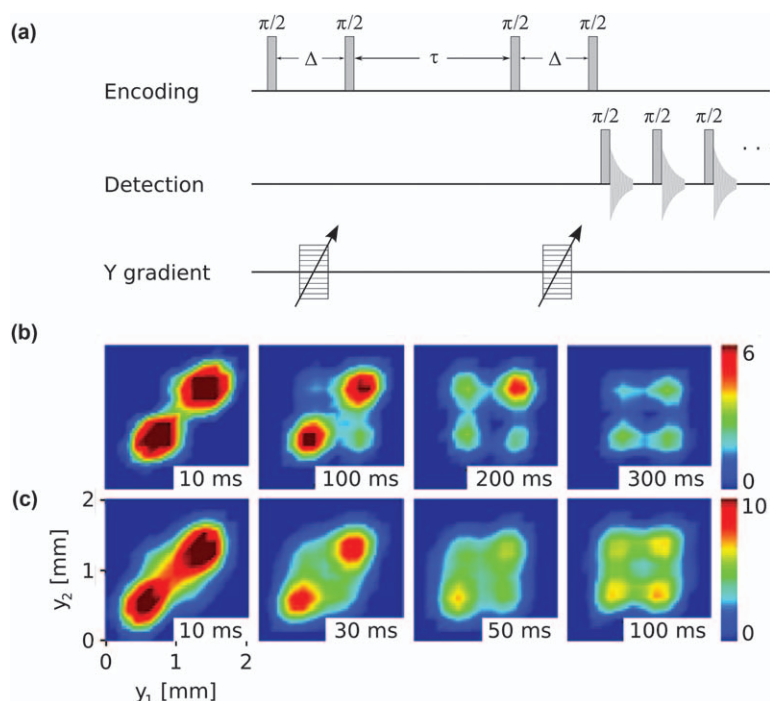


Figure 25.6 Quantifying gas diffusion through a membrane using position correlation. (a) Pulse sequence, consisting of two phase encoding steps separated by mixing time τ . Although readout was performed stroboscopically, data was not analyzed time resolved. Instead, only the snapshots containing encoded gas were considered for analysis, hence improving the sensitivity. (b) Position correlation images for membrane with 20 nm pores. τ is shown on each of the panels. y_1 denotes the encoding position perpendicular to the membrane during the first, y_2 during the second phase encoding step. The diffusion time constant was determined as $D = 1.54 \times 10^{-7} \text{ m}^2 \text{ s}^{-1}$. (c) Position correlation images for membrane with 200 nm pores; $D = 7.5 \times 10^{-7} \text{ m}^2 \text{ s}^{-1}$. Adapted with permission from ref. 11. Copyright 2007 American Chemical Society.

diffusion constant for the two membranes, which differed by about a factor five.

25.5.4 Multiplicative Noise

Since remote detection is inherently a point-by-point technique, the signal is affected by multiplicative noise more strongly than when detected transiently. Multiplicative noise denominates noise that is caused by non-reproducibility of the experiment. It only affects the signal and is, to first order, proportional to the signal. If no signal is detected, this type of noise is absent. It does not affect the detection limit of an experiment, but it puts an upper limit to the achievable sensitivity. With transient detection of an interferogram and subsequent Fourier transform, only the phase and the amplitude of a resonance are affected. Spectral regions without any signal essentially show a noise level corresponding to the electronic noise of the detector, and weak signals are not affected by the multiplicative noise of strong signals. With remote detection, each data point is affected by the multiplicative noise of the total signal. After Fourier transform of the interferogram, this noise gets distributed over the whole spectrum. Therefore, spectral regions with only weak signals or no signal at all experience the same noise level that is dominated by the multiplicative noise of the strong signals. This noise behavior is analogous to the indirect dimension in a 2D NMR experiment, which is also affected by multiplicative noise.²⁹

To demonstrate the potential significance of multiplicative noise, the TOF signal following the inversion of spin magnetization in an encoding volume is shown in Figure 25.7a. The experiment was repeated 100 times, which allowed the estimation of a standard deviation for each data point (Figure 25.7b). It is evident that in t_{TOF} regions with weakly changing signal, the noise level is considerably lower. Since the noise is multiplicative, increasing the ^{129}Xe polarization would not improve the sensitivity. However, with decreasing sensitivity, at some point the additive thermal noise would become dominant. From the shape of the noise level, it could be concluded that fluctuations of the flow rate were the dominant noise contribution.

A remedy for multiplicative noise is, for example, the selective excitation of weak signals to avoid these signals being covered by the noise caused by strong signals.¹⁸ The best strategy is to minimize multiplicative noise in the first place by a careful design of the experimental setup, since this type of noise is predominantly caused by fluctuations of experimental parameters such as the external magnetic field, the pulse amplitude to excite the spins or, as shown above, the flow velocity of the carrier. This last influence can be reduced by collecting all the encoded fluid at once in a detection volume that is slightly larger than the encoded fluid volume to make sure all the fluid is in the detector upon readout. In an experiment with TOF, adding up all the snapshots, including a few forerunning and overrunning snapshots, also reduces this type of noise.

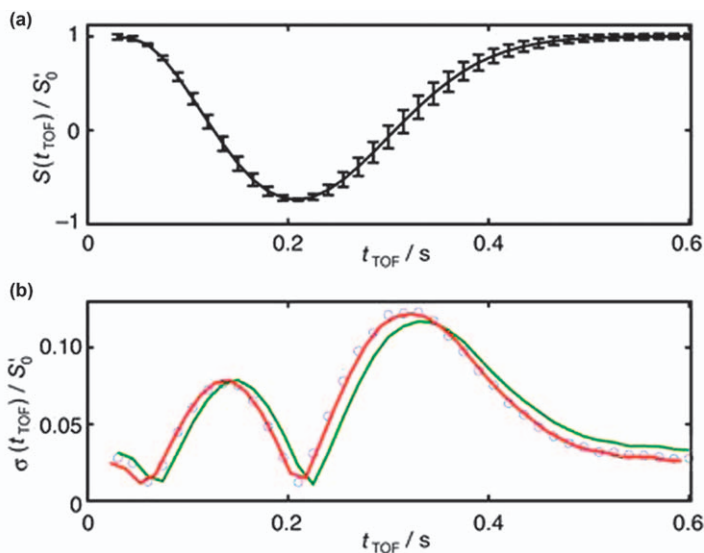


Figure 25.7 Multiplicative noise with remote detection. Hyperpolarized ^{129}Xe gas was encoded with an inverting 180° pulse. As it was flowing out of the encoding volume, its longitudinal magnetization was recorded stroboscopically using a second, smaller coil. (a) Relative amplitude of the longitudinal magnetization of ^{129}Xe as a function of time after the encoding step. S'_0 represents the signal of unencoded gas. The error bars represent the standard deviation of an individual measurement for the different TOF data points. (b) Standard deviation of signal amplitude as a function of t_{TOF} . The experimental data points (o) were fitted with a multiplicative contribution, caused by fluctuations of the mean volumetric gas flow rate $\langle Q \rangle$, and an additive contribution, caused by thermal electronic noise. The green curve was obtained under the assumption of an idealized multiplicative noise contribution caused purely by flow fluctuations. A relative standard deviation $\sigma_Q/\langle Q \rangle = 0.032$ was obtained. The red curve with $\sigma_Q/\langle Q \rangle = 0.034$ was obtained by allowing some flexibility for the different terms in the model relative to each other,²⁹ which is justifiable given that flow rate fluctuations cause second order effects, such as altered T_2^* or resonator quality factors. For both fits the additive noise contribution was fixed to the experimental value, $\sigma_+ / S'_0 = 0.01$.

25.6 Concluding Comments

Remote detection can offer huge sensitivity gains for certain experimental situations. Problems that are unfavorable for conventional NMR methodology tend to be most suitable for this technique. This includes the analysis of samples that require a low magnetic field, porous materials with large internal susceptibility gradients or very low filling factors, and microfluidic devices. Flow studies are particularly suitable, since the loss of the transient spectral or imaging dimension and the corresponding inherent increase of the experiment time can be compensated by introducing flow as

the new transient dimension. This not only remedies to some degree the increased experiment time, it offers a complementary way to study flow. Rather than measuring local velocity vectors as in conventional pulsed gradient spin-echo experiments, flow and dispersion is measured in an external laboratory frame of reference.

Remote detection has proved to be especially useful to study flow in microfluidic devices. These pose the problem that large, insensitive coils are required to accommodate the device, but the actual fluid volume is very small. The combination of commercial probes for encoding and dedicated probes or circuits for detection, using an optimized coil with a high filling factor, turned out to be quite practical. Furthermore, the low dispersion in these devices sometimes allow one to regain another transient dimension by correlating the time-of-flight with a spatial location,³⁰ and the known geometry of the fluid channels facilitates very effective compressive sampling schemes.³¹ Eventually, continued advances in the area of microfluidics, such as the recent development of an optical ¹²⁹Xe polarizer on a chip,³² will open up further opportunities for the use of remote detection.

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